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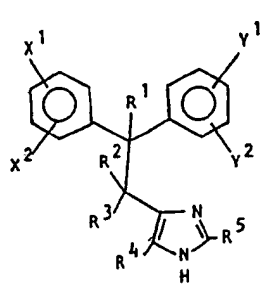
(54) Derivatives of imidazole, their preparation and utilisation, and pharmaceutical compositions containing these derivatives.

(57) Derivatives of imidazole corresponding to formula I



I

wherein X^1, X^2, Y^1 and Y^2, whether or not identical, can have different significancies, R^1 is hydrogen, a methyl or phenyl group, R^2 and R^3, whether or not identical, represent hydrogen, a hydroxyl, alkyl or alkoxy group, it being possible for R^1 and R^2 together to represent a carbon-carbon bond, R^4 and R^5, whether or not identical, being hydrogen or alkyl, and the tautomers and salts of these compounds, also the pharmaceutical compositions containing them.

The compounds are endowed with α_2-blocking and/or anti-convulsive activities and are utilisable as therapeutic agents for man.

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Derivatives of imidazole, their preparation and utilisation, and pharmaceutical compositions containing these derivatives.

The present invention relates to derivatives of imidazole and to their salts of addition with pharmaceutically utilisable acids, the processes for their preparation and pharmaceutical compositions containing at least one of these derivatives or its salt of addition, and their utilisation as blocking agents of α_2-adrenergic receptors and as agents possessing an anti-convulsive activity.

α-adrenergic receptors are subdivided into α_1 and α_2 receptors essentially on the basis of their response to specific antagonistic agents, and it has been found that α_2 receptors are located at the level of the noradrenergic nerve endings where they are involved in the " release " of noradrenaline, and that there exist α_2 receptors which are present in various tissues as for example in the pancreas, the blood platelets, the adipose tissues, the blood vessels.

In view of their biological activities, selective α_2 receptor blocking agents may be of great therapeutical interest for the treatment of depressive illness and of cerebral ageing, such as senile dementia, some cardiac deficiencies and asthma, and for the prophylactic and curative treatment of ailments in which platelet hyper-aggregability is involved, such as migraine and thrombotic ailments.

Further said compounds may be of great value for the treatment of metabolic troubles such as diabetes and obesity, of sexual inadequacies, of certain forms of hypertension and as anorexigenic and diuretic agents.

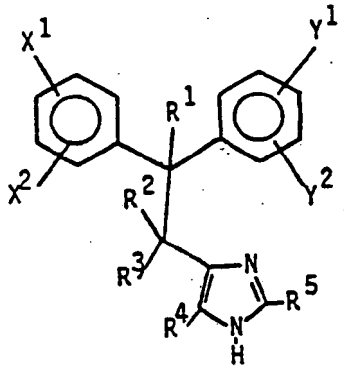
Although the existence of α_2-adrenergic receptors was described several years ago, at present very few compounds possessing selective α_2-blocking activity are known. The agents most described and most cited in literature are yohimbine and rauwolscine, but these products lack selectivity and possess numerous side-effects which prevent their use as therapeutics. The other products described in recent literature are experimental compounds of which little is known as regards their real therapeutic potential. Among these compounds there are derivatives of imidazoline such as those described in British Patent n° 2,068,376, British Patent Application n° 2,102,422 A and EP 0092,328.

In this class of derivatives, 2-[2-(1,4-benzodioxanyl)] -2-imidazoline hydrochloride (Idazoxan hydrochloride) seems to be the compound of greatest interest.

Another class of compounds is that containing an imidazole group, especially 2-[2-(1,4-benzodioxanyl)alkyl]-imidazoles, described by L.M.Caroon et al.[J.Med.Chem., 25, 666-670 (1982)] and 4-(phenylalkyl)imidazoles, 4-(phenylalkanoyl) imidazoles and 4-[(phenyl)-hydroxy-alkyl]- imidazoles described in European patent application EP 0,034,473.

The Applicants have discovered a new class of imidazole derivatives which has proved to present particular interesting biological activities.

The present invention includes the imidazole derivatives which respond to the general formula I



I

wherein :

X^1, X^2, Y^1 and Y^2, which may or may not be identical, represent hydrogen, a halogen such as fluorine, chlorine or bromine, a linear or branched alkyl radical C_1, C_2 or C_3, a linear or branched alkoxy radical C_1, C_2 or C_3, a carboxy group, an alkoxy[C_1, C_2 or C_3]-carbonyl group or a phenyl group,

R^1 represents hydrogen, a methyl or phenyl group,

R^2 and R^3, which may or may not be identical, represent hydrogen, a hydroxyl group, an alkyl group C_1, C_2, C_3, C_4, C_5 or C_6, linear or branched, a linear or branched alkoxy group C_1, C_2, C_3 or C_4,

R^1 and R^2 may together likewise represent a carbon-carbon bond, which signifies that the carbon atoms α and β are connected by a double bond, as represented by the

general formula I' on page 50,
R^4 and R^5, which may or may not be identical, represent hydrogen or a linear or branched alkyl radical C_1, C_2, C_3, also the corresponding geometric isomers, in the pure form or in the form of a mixture, and the corresponding optically pure isomers, racemic or non-racemic mixtures of these isomers, the various possible tautomers, also the salts of addition of these compounds formed with pharmaceutically utilisable acids.

A preferred class of the compounds corresponding to the general formula I is that in which :
X^1, X^2, Y^1 and Y^2, which may or may not be identical, represent hydrogen, an atom of fluorine or chlorine, a methyl, methoxy or phenyl radical,
R^1 represents hydrogen or a methyl group,
R^2 represents hydrogen, a hydroxyl, methyl or methoxy group,
R^1 and R^2 may together represent a carbon-carbon bond,
R^3 represents hydrogen or a linear or branched alkyl group C_1, C_2, C_3 or C_4,
R^4 and R^5, which may or may not be identical, represent hydrogen or a methyl group.

A particularly interesting class of compounds responding to the general formula I is that in which :
X^1, X^2, Y^1 and Y^2, which may or may not be identical, represent hydrogen, an atom of fluorine or chlorine a methyl, methoxy or phenyl radical, R^1, R^2, R^3 , R^4 and R^5 represent hydrogen, and R^1 and R^2 may together likewise represent a carbon-carbon bond.

Another particularly interesting class of compounds which respond to the general formula I is that in which :
X^1, X^2, Y^1, Y^2, R^1, R^4 and R^5 represent hydrogen,

R^2 represents hydrogen or a linear or branched alkoxy radical C_1, C_2 or C_3

R^3 represents hydrogen or a linear or branched alkyl radical C_1, C_2 or C_3, and

R^1 and R^2 can together equally represent a carbon-carbon bond.

Examples of compounds according to the invention are :

4(5) - (2,2-diphenyl ethyl) imidazole,

4(5) -[(2,2-diphenyl-1-methyl) ethenyl] imidazole,

4(5) -|[2-(3-methylphenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(2-chlorophenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(4-fluorophenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(2-fluorophenyl)-2-(4'-fluorophenyl)] ethyl | imidazole,

4(5) -|[2-(4-methoxyphenyl)-2-phenyl] ethyl | imidazole,

4(5) -[(2,2-diphenyl-1-n.propyl) ethenyl] imidazole,

4(5) -[2-(1,1-diphenyl)-pentyl] imidazole,

4(5) -[2-(1,1-diphenyl-2-methoxy) pentyl] imidazole,

4(5) - (2,2-diphenylethyl)-2-methylimidazole,

4(5) - (2,2-diphenylethyl)-5(4)-methylimidazole.

4(5) -|[2-(2-fluorophenyl)-2-(6'-fluorophenyl)]ethyl | imidazole,

4(5) -|[2-(2-fluorophenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(4-biphenyl)-2-phenyl] ethyl | imidazole,

4(5) - [1-(2,2-diphenyl)-propyl] imidazole,

4(5) -|[2-(2-methylphenyl)-2-(5'-methylphenyl)]ethyl| imidazole

4(5) -|[2-(2-methylphenyl)-2-(4'-methylphenyl)] ethyl| imidazole.

The products according to the invention may likewise be present in the form of a salt of addition with a pharmaceutically utilisable acid, such as an inorganic acid such for example as hydrochloric acid, sulphuric acid or phosphoric acid, or an appropriate organic acid such as an aliphatic, cycloaliphatic, aromatic, araliphatic or heterocyclic, carboxylic or sulphonic acid, such for example as formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, hydroxybenzoic, salicylic, phenylacetic, mandelic, embonic, methanesulphonic, ethanesulphonic, pantothenic, toluenesulphonic, sulphanilic, cyclohexylaminosulphonic, stearic, alginic, β-hydroxybutyric, malonic, galactaric, galacturonic acid.

If the derivatives of formula I are present in the form of salts of addition with acids, they can be transformed according to usual processes into free bases or into salts of addition with other acids.

The compounds of formula I in which R^1 and R^2 together represent a carbon-carbon bond can be present in the form of cis-trans geometric isomers, or in the form of pure isomers, or in the form of a mixture in equal or unequal proportions.

The compounds of formula I can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical, racemic or diastereo isomers; all these forms form part of the present invention

The products according to the invention comprising one or more centres of asymmetry can be utilised either in the form of mixtures containing several diastereo isomers, whatever are the relative proportions thereof, or in the form of pure diastereo isomers.

Furthermore the pairs of enantiomers can be present in equal proportions (racemic mixtures) or unequal proportions.

Finally the product can be utilised in the form of an optically pure compound.

The optical isomers can be obtained by resolution of the racemic compounds according to conventional processes, for example by formation of diastereoisomer salts by treatment with optically active acids, such as tartaric, diacetyltartaric, tartranilic, dibenzoyltartaric, ditoluoyltartaric acid, and separation of the mixture of diastereo isomers, for example by crystallisation or chromatography, followed by liberation of the optically active bases from these salts.

The optically active compounds according to formula I can likewise be obtained by utilising optically active starting products.

The present invention also covers pharmaceutical compositions containing, as active ingredient, at least one compound of the general formula I or its salt of addition with a pharmaceutically utilisable acid, in the presence or absence of an excipient utilised in Galenic pharmacy.

These compositions are prepared in such manner that they can be administered by oral, rectal, parenteral or local route.

They can be solids, liquids or gels and be presented, according to the administration route, in the form of powders, tablets, lozenges, coated tablets, capsules, granulates, syrups, suspensions, emulsions, solutions, suppositories or gels. These compositions can likewise comprise another therapeutic agent having an activity similar to or different from that of the products of the invention.

In order to facilitate administration, these pharmaceutical compositions can be presented in the form of unit doses.

The products according to the invention are in general endowed with selective α_2-blocking properties. Consequently, as indicated, these products can be of major interest in the treatment of depressive and degenerative diseases of the central nervous system.

It is also possible to envisage their utilisation as anti-migraine, antithrombotic, antiasthmatic, diuretic, anorexigenic and antidiabetic agents and for the treatment of certain forms of hypertension, obesity, certain cardiac diseases or sexual inadequacies.

Certain compounds according to the invention also possess interesting pharmacological activities concerning the central nervous system, for example an anticonvulsive activity, whether or not associated with an effect on α-adrenergic receptors.

Thus the utilisation of the products of this type can be envisaged in the treatment of various forms of epilepsy and dyskinesia.

Some compounds have also been observed to block biogenic amines uptake by rat synaptosomes, which emphasizes their possible interest as anti-depressants.

The Applicants have discovered that certain products according to the invention possess α_2-agonist properties which render them of interest for the treatment of gastroduodenal ulcers and certain forms of hypertension.

The compounds according to the invention are prepared according to several processes which are part of the present invention and are described below. In the case where these processes give rise to the production of new intermediate compounds, these as well as the processes serving for their preparation likewise form part of the present invention.

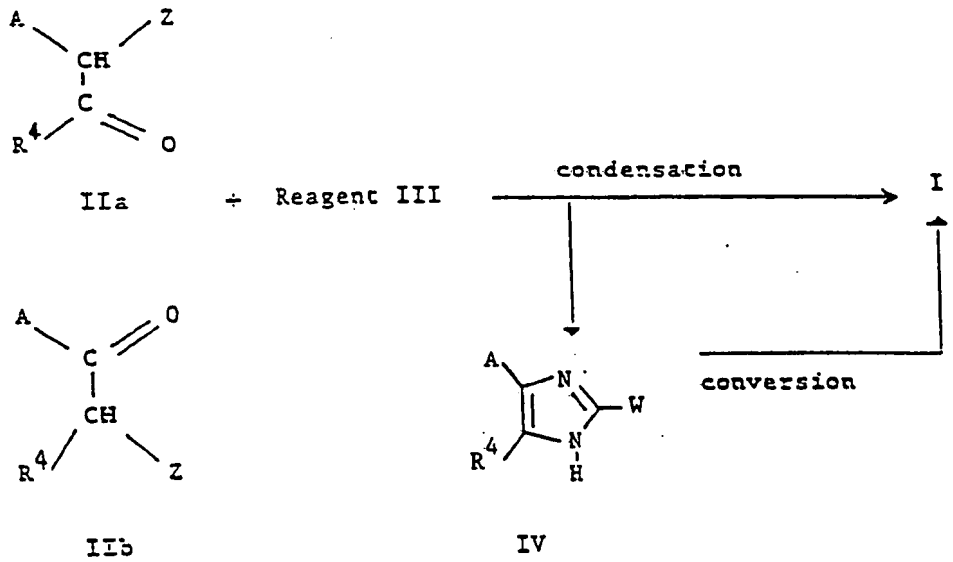
1. According to a first process, the compounds of formula I are obtained by synthesis of the imidazole group from an adequate starting product.

Several methods are known for carrying out the synthesis of the imidazole group, as described e.g. by H.Bredereck et al. [Angewandte Chemie, 71, 759-764 (1959)] and by M.R.Grimmett [Advances in Heterocyclic Chemistry, Ed. A.R.Katritzky and A.J.Boulton, Academic Press, Vol.12, 104-137 (1970) and Vol.27, 242-269 (1980)].

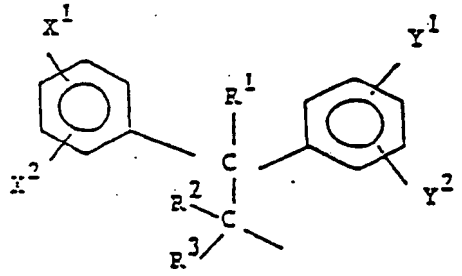
Some of these methods are indicated below by way of non-limitative examples.

1.1. According to a first procedure, the compounds of formula I are obtained by condensation of a carbonyl derivative of formula IIa or IIb, the carbonyl group of which may be latent, for example in the form of an acetal or thiocetal, whether or not cyclic, with a nitrogenous reagent III, followed if appropriate by a complementary conversion according to Diagram 1.1. below.

Diagram 1.1.



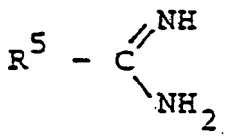
In this diagram, A represents the group



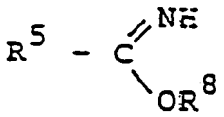
X^1, X^2, Y^1, Y^2 and R^1 to R^4 having the values defined above, Z represents a function such as a hydroxy radical, an oxoradical, an atom of halogen, an amino group, an alkancyloxy radical,

W represents a substituent which is easily eliminated, for example by hydrolysis, hydrogenation, desulphurisation, hydrogenolysis, diazotisation or oxidation, such as a mercapto or amino group,

and the reagent III represents a nitrogenous compound or a combination of two compounds at least one of which is nitrogenous, as for example an amide of formule $R^5 - CONH_2$, an amidine of formula



or an iminoether of formula



in the presence or absence of ammonia, cyanamide, guanidine, an alkaline or ammonium thiocyanate, or formaldehyde in the presence of ammonia.

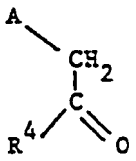
In the above formulae R^5 possesses the values defined previously and R^8 is an alkyl group C_1-C_3.

Hereinafter the symbols A, Z, W and R^1 to R^8 always possess the values as defined above, except where explicitely indicated.

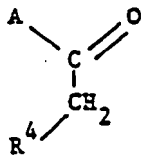
The choice of the reagent III and of the experimental conditions take place according to the nature of the group Z of the molecule IIa or IIb.

Thus in the case where Z represents an atom of halogen or an oxo-, hydroxyl, alkanoyloxy or amino radical, the synthesis of a compound of formula I is effected by condensation of the compound IIa or IIb with an amide of formula R^5— $CONH_2$ which is often likewise used as solvent, at an elevated temperature which may reach the reflux temperature, under an inert atmosphere or advantageously under an atmosphere of ammonia.

A very practical variant of this process consists in preparing the α-halocarbonyl derivative of formula IIa or IIb (Z = halogen) <u>in situ</u>, for example by bromination of a carbonyl derivative of formula Va or Vb,



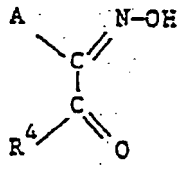
Va



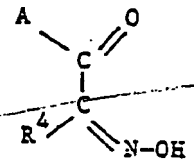
Vb

in formamide, followed by its condensation with formamide by heating of the reaction medium.

Another interesting variant consists in generating an α-amino-carbonyl derivative of formula IIa or IIb (Z = NH_2) in situ, by catalytic reduction in formamide or acetamide, of an oxime of formula VIa or VIb,



VIa

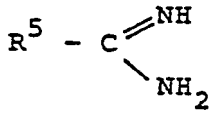


VIb

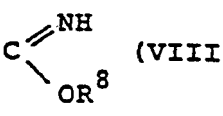
which can easily be obtained for example by conversion of a carbonyl derivative of formula Va or Vb into a nitroso compound according to known methods.

The use of an amide $R^5 - CONH_2$ as reagent III gives very good results in the case where R^5 represents hydrogen or a methyl radical, but less good results if R^5 is an alkyl group C_2-C_3.

The variant of the process utilising an amidine



(VII) or an iminoether



(VIII)

as reagent does not present this drawback, and enables to obtain, with good yields, derivatives of formula I in which R^5 represents either an atom of hydrogen or an alkyl radical C_1-C_3.

In the usual way, the amidine and the iminoether are used in the form of salts of addition with an acid, for example in the form of hydrochloride or acetate.

The condensation proceeds easily by mixing the reagents IIa or IIb and VII or VIII in a suitable solvent such as an alcohol, in the presence of ammonia and/or a strong

base such for example as an alcoholate of an alkaline, the reaction medium advantageously being heated.

Another way to transform an α-aminocarbonyl derivative of formula IIa or IIb (Z = NH_2) into a compound of formula I consists in the condensation of the compound IIa or IIb with a potassium thiocyanate followed by the complementary conversion of the intermediate IV (W = SH) formed (of. Diagram 1.1.). The condensation is effected easily by heating a mixture of the two reagents in a solvent such as water and the intermediate IV (W = SH) is then converted into a derivative of formula I, for example by oxidation.

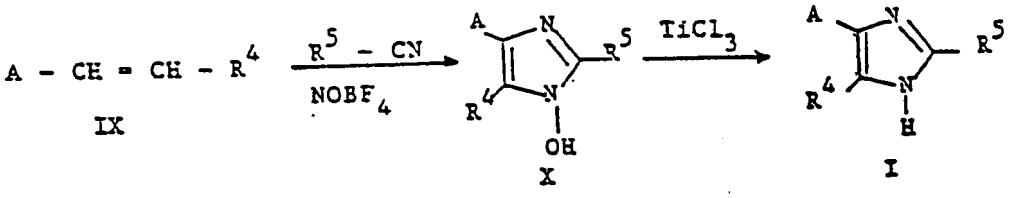
This can be done for example by treating the intermediate IV in aqueous medium with nitric acid at a moderate temperature.

1.2. The imidazole nucleus can likewise be formed from an alkene of formula IX

$$A - CH = CH - R^4 \qquad IX.$$

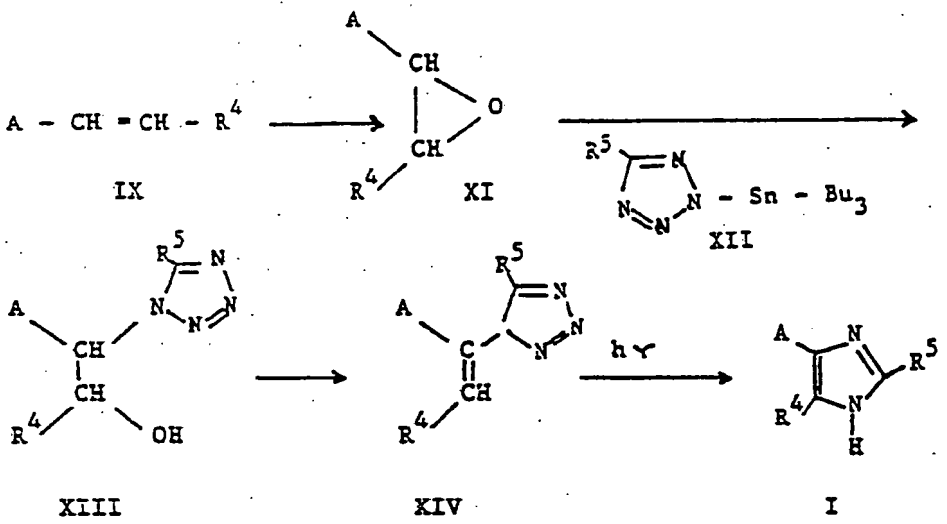
The alkene IX is transformed into a derivative of formula I by treatment with nitrosonium tetrafluoroborate in the presence of a nitrile of formula R^5—CN utilised likewise as solvent, followed by a complementary conversion of the intermediate X with the aid of titanium trichloride, in accordance with Diagram 1.2.a.

Diagram 1.2.a.



An alkene of formula IX can likewise lead to a derivative of formula I, as indicated in Diagram 1.2.b.

Diagram 1.2.b.



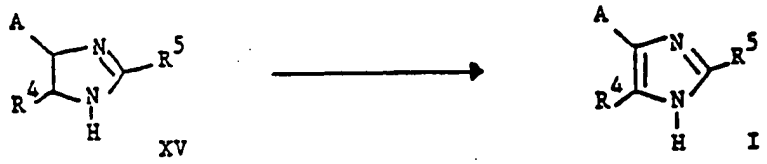
The alkene IX is converted by conventional methods into an epoxide of formula XI which is condensed with a tri-n.butylstannyl tetrazole of formula XII, obtained from a nitrile R^5 - CN and tri-n.butyl tin azide, by opposing the reagents XI and XII in an inert solvent such as diethyl ether, at room temperature, followed by a treatment with gaseous hydrochloric acid.

The alcool XIII obtained is dehydrated in vinyl tetrazole XIV, for example by means of triphenoxyphosphonium iodide in N,N-dimethyl formamide at room temperature, this dehydration being followed by a treatment by an alkaline hydroxide in aqueous solution.

The irradiation, advantageously at 254 nm, of the intermediate XIV in an appropriate solvent such as an alcohol or a hydrocarbon possibly in the presence of an acid as catalyst, supplies the compound I with good results.

1.3. Another interesting manner of synthesising the imidazole group can be carried out starting from a heterocyclic group. Thus the compounds of formula I are obtained starting from an imidazoline of formula XV in accordance with Diagram 1.3.a.

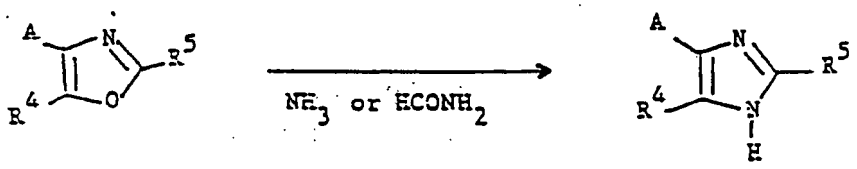
Diagram 1.3.a.



The transformation of the imidazoline XV is effected either by means of an appropriate oxidising reagent, such for example as manganese dioxide in an inert solvent such as acetone, at moderate temperature, or by dehydrogenation, carried out at elevated temperature (> 150°C) in an inert solvent with the aid of an appropriate catalyst, such as a catalyst based upon nickel, platinum or palladium and possibly in the presence of a co-reagent such as copper oxide or sulphur.

Starting from an oxazole of formula XVI, the compounds of formula I are easily obtained according to Diagram 1.3.b. by heating the oxazole XVI in the presence of ammonia or advantageously in the presence of formamide.

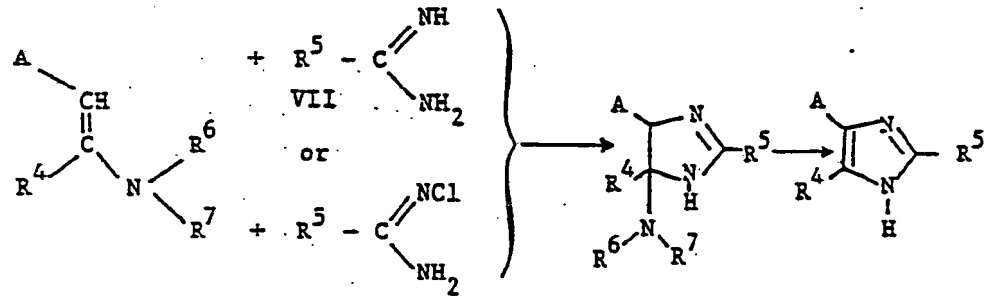
Diagram 1.3.b.



XVI I

1.4. Another way of synthesising the imidazole group consists in condensing an enamine of formula XVII with an amidine VII or with an N-chloro-amidine XVIII in accordance with Diagram 1.4..

Diagram 1.4.



XVII XVIII XIX I

$R^6 \diagdown R^7 \diagup N$ - represents the amino group of the enamine, such for example as a dialkylamino or morpholino group.

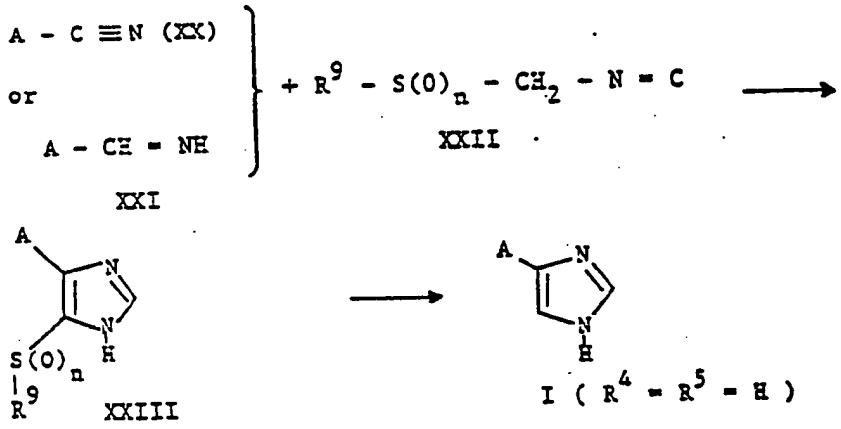
The condensation takes place under an inert atmosphere, under anhydrous conditions, in the case of an amidine in the presence of an equimolar quantity of bromine, in an inert solvent such as dichloromethane and advantageously in the

presence of an organic base such as triethylamine or pyridine.

The intermediate aminoimidazoline XIX is deaminated into a derivative of formula I, either already *in situ* under the utilised reaction conditions, or by heating the intermediate XIX in the presence of triethylamine hydrochloride or pyridine hydrochloride.

1.5. A last method mentioned below for the synthesis of the derivatives of formula I (R_4 = R_5 = hydrogen) by formation of the imidazole group consists of the condensation of a nitrile XX or of an aldimine XXI with an isonitrile of formula XXII, in accordance with Diagram 1.5..

Diagram 1.5.



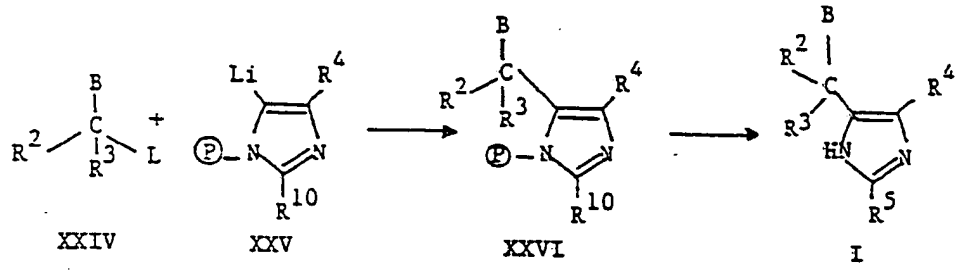
In this diagram, A possesses the value defined above, n is equel to 0 or 2 (condensation with a nitrile XX) or n is equel to 0 (condensation with an aldimine XXI) and R^9 represents a methyl or tolyl group.

The condensation is effected under anhydrous conditions by opposing the reagents in an inert solvent such as tetrahydrofuran (THF) at room temperature in the presence of a strong base, as for example potassium tert.-butoxide; a consecutive treatment with water furnishes the intermediate XXIII. If the nitrile XX is subject to steric hindrance the condensation is most advantageously effected by opposing this nitrile to the anion of XXII generated by means of butyl lithium in anhydrous THF at low temperature. The intermediate XXIII is converted into a compound of formula I (R^4 = R^5 = hydrogen), for example by desulphurisation by means of hydrogen in the presence of Raney nickel.

2. According to a second process, the compounds according to the invention are obtained by grafting of the imidazole group on to a suitable substrate.

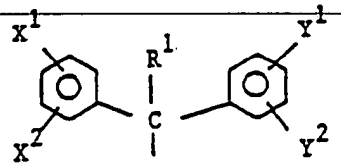
2.1. A first procedure, illustrated by Diagram 2.1., consists in substituting the group L of a compound of formula XXIV by an imidazole group, in general utilised in the form of an organolithiated derivative of formula XXV.

Diagram 2.1.



XXIV XXV XXVI I

In this diagram B represents the group



L is an easily substitutable radical such as a halogen like chlorine, bromine, iodine, an O-tosyl group or an O-mesyl group.

Ⓟ represents a protective group such for example as an alkyloxymethyl, benzyloxymethyl, dialkoxymethyl, trimethylsilylmethyl, [2-(trimethylsilyl) ethoxy] methyl, trityl, vinyl, benzyl, N,N-dialkylaminosulphonyl, 2-chloroethyl, 2-phenylsulphonylethyl, diphenyl methyl or [(bistrifluoromethyl) (4-chlorophenoxymethoxy)] methyl radical, R^{10} represents the group R^5 or a group substitutable by hydrogen, such for example as a phenylthio or alkylthio group.

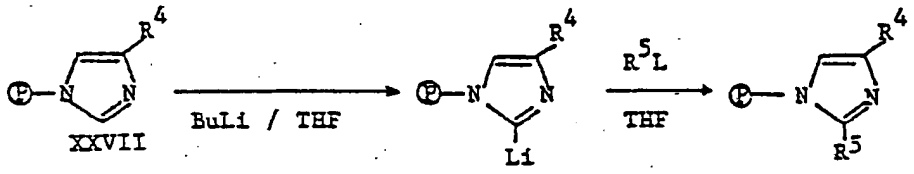
Hereinafter the radicals X^1, X^2, Y^1, Y^2, R^1 to R^{10}, B, L and Ⓟ represent the values as defined previously, unless otherwise explicitely stipulated.

The organolithium derivative XXV is prepared by lithiation of an N-protected imidazole and substituted in the 2 position by a group R^{10}, provided that R^{10} does not represent hydrogen, by means of n-butyl lithium at low temperature, under an inert atmosphere and in an inert solvent such as diethyl ether or THF.

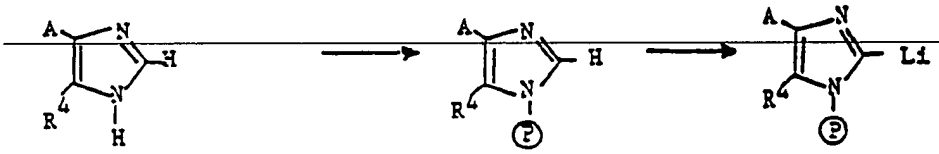
The substitution of the L group of the substrate XXIV proceeds by addition of this compound at low temperature, in solution in an appropriate solvent such as THF, anhydrous diethyl ether or a saturated hydrocarbon, to the solution of the lithiated reagent XXV.

After reaction the mixture is brought to room temperature, treated by a protic solvent such as water, and acidified to supply either the desired derivative of formula I directly or the intermediate of formula XXVI which by deprotection is converted into a compound of formula I.

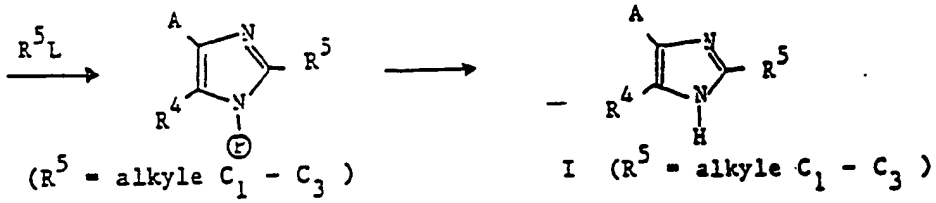
The protection of the imidazole group in the 2 position by a phenylthio or alkylthio group is effected by lithiation of an N-protected imidazole, followed by a reaction with an alkyl disulphide or a phenyl disulphide under conditions similar to those described for the substitution of the imidazole group in the 4 position. The same procedure can be utilised for the introduction of the group R^5, R^5 being an alkyl radical C_1-C_3, into an imidazole of formula XXVII, utilising a reagent of formula R^5 L in which R^5 is an alkyl radical C_1-C_3, according to the following diagram, L and Ⓟ being defined above.



Of course the above-stated procedure can likewise be utilised for the conversion of a derivative of formula I in which R^5 represents hydrogen into a derivative of formula I in which R^5 represents an alkyl group C_1-C_3 according to the following diagram :

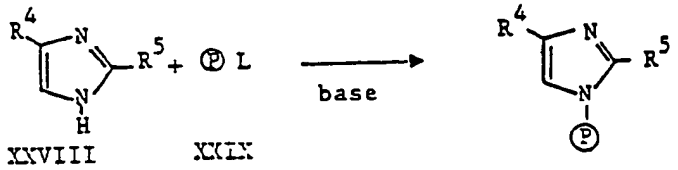


I



(R^5 = alkyle C_1 - C_3) I (R^5 = alkyle C_1 - C_3)

The protection of the nitrogen of the imidazole group is effected according to known methods, for example by treatment of the imidazole XXVIII in the presence of a base in a solvent such for example as dimethyl formamide or 1,2-dichloroethane in the presence of a phase transfer catalyst, with a reagent of formula Ⓟ L (XXIX), Ⓟ and L being defined above, according to the diagram :



XXVIII XXIX

The deprotection of the imidazole group is effected by known methods :

the radical R^{10}, being an alkylthio or phenylthio group, is substituted by hydrogen, for example, by a desulphurisation by means of hydrogen at elevated temperature in the presence of a catalyst such as Raney nickel,

the radical Ⓟ is substituted by hydrogen by different methods selected as a function of the nature of Ⓟ, such for example as :

(a) by acidolysis in aqueous or non-aqueous medium by means of an acid such as a halogenated hydracid, acetic acid, trifluoroacetic acid, sulphuric acid, at a temperature which can vary from room temperature to reflux temperature,

(b) by treatment with tetra-n.butylammonium fluoride in THF at room temperature,

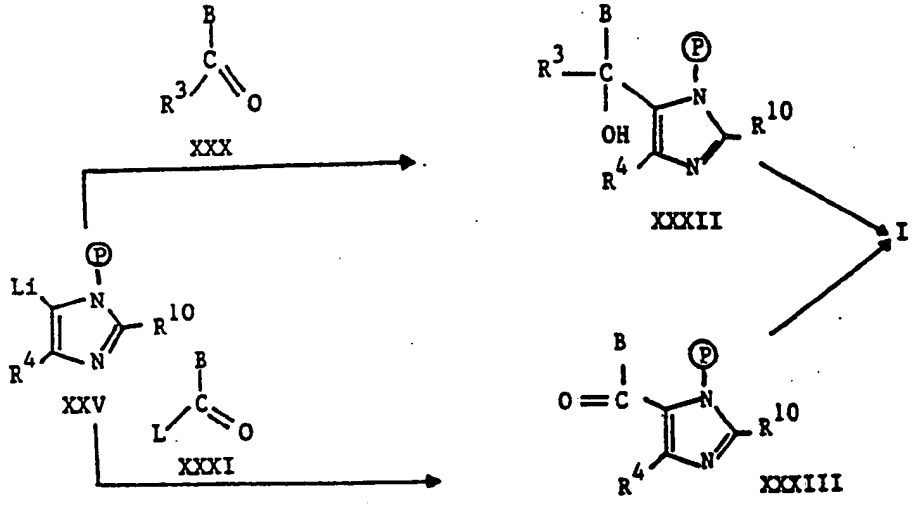
(c) by treatment with sodium hydride in dimethyl formamide at room temperature, followed by hydrolysis,

(d) by catalytic hydrogenation (hydrogenolysis),

(e) by treatment with sodium hydride, followed by hydrolysis and reaction at elevated temperature with sodium acetate in acetonitrile.

2.2. According to a second procedure, the derivatives of formula I are obtained by condensation of an organolithiated derivative XXV with a carbonyl derivative of formula XXX or XXXI followed by a deprotection and possibly a complementary conversion, in accordance with Diagram 2.2..

Diagram 2.2.



The experimental conditions of the condensation and the deprotection are the same as those described in paragraph 2.1.. Any complementary conversion to obtain a derivative of formula I from the intermediates XXXII and XXXIII can be effected in one or more steps, from deprotected, partially deprotected or protected intermediates, according to conventional methods selected as a function of the nature of the intermediate and of the compound I to be obtained, as for example :
(a) by dehydration of XXXII (this method is of particular interest for obtaining a derivative of formula I in which R_1 and R_2 together represent a carbon-carbon bond, possibly followed by a hydrogenation of the alkene of formula I into another compound of formula I (R_1 and R_2 = hydrogen),

(b) by alkylation, for example by means of a reagent of formula $(R^{11}O)_2SO_2$ or $R^{11}X$ wherein R^{11} represents a linear or branched alkyl radical C_1-C_4 and X possesses the values defined above (easy method for the preparation of derivatives of formula I in which R^2 represents an alkoxy group C_1-C_4),

(c) by substitution of the hydroxyl radical by a halogen, such as chlorine or bromine, by means of an halogenating agent such as PBr_5 or $SOCl_2$, and conversion of this alkyl halide by hydrogenolysis,alkylation or by dehydrohalogenation into a compound of formula I,

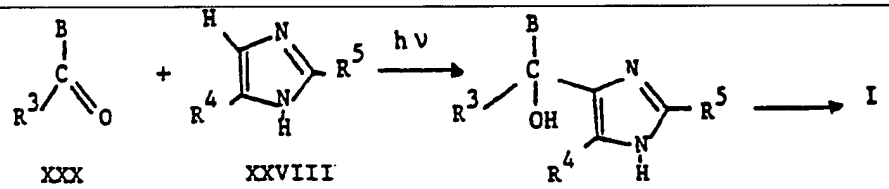
(d) by hydrogenolysis,

(e) by reduction of an intermediate of formula XXXII or XXXIII,

(f) by alkylation of a derivative of formula XXXIII by the expedient of an organometallic derivative, such as an organomagnesium compound of formula $R^{12}MgX$ or an organolithium compound of formula $R^{12}Li$, R^{12} being a linear or branched alkyl radical C_1-C_6, followed if necessary by one or more of the above conversions in order to obtain the desired derivative of formula I.

2.3. According to a variant of this process, the derivatives of formula I are likewise obtained by photochemical addition of an imidazole derivative XXVIII, possibly in its form protected by the radicals R^{10} and/or Ⓟ defined above, to a carbonyl derivative of formula XXX, followed if appropriate by a complementary conversion and/or a deprotection in order to obtain a compound of formula I, according to Diagram 2.3.

Diagram 2.3.



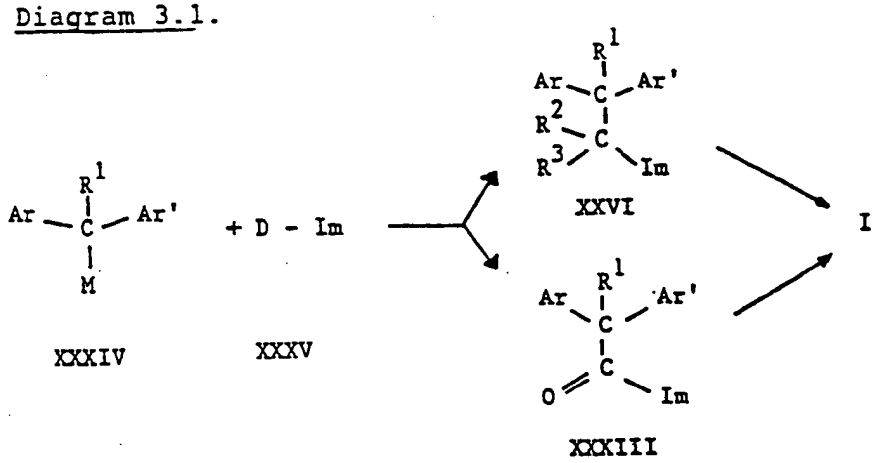
XXX XXVIII

B, R^3, R^4 and R^5 possess the values defined above.
The addition is produced by irradiation under inert atmosphere either of a solution of the reagents in an inert solvent such as acetonitrile, or of a mixture of the reagents at room temperature or in gaseous phase.
The complementary conversion and the deprotection take place as described above.

3. According to a third procedure, the derivatives of formula I are obtained by coupling of two suitable reagents by effecting a carbon-carbon bond.

3.1. According to a first method, the carbon-carbon bond is realised by condensation of an organometallic derivative XXXIV with a halogenated or carbonyl derivative XXXV, such as a ketone, an aldehyde, an ester or an acid halide, according to Diagram 3.1. below.

Diagram 3.1.

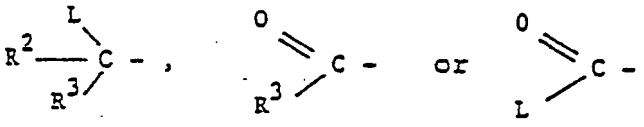


XXXIV XXXV XXVI XXXIII

In this diagram:

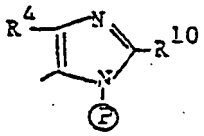
M represents an atom of a metal such as lithium, sodium or potassium or a radical containing a metal such as magnesium, as for example MgCl or MgBr, zinc, copper or titanium,

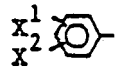
D represents a halogenated or carbonyl group such as

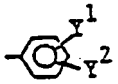
 wherein

L represents an atom of chlorine, bromine or iodine,

Im represents the imidazole group of formula

 protected by a radical Ⓟ in the 1-position and a radical R^{10} in the 2-position in which Ⓟ and R^{10} possess the values defined above,

Ar represents the group 

Ar' represents the group 

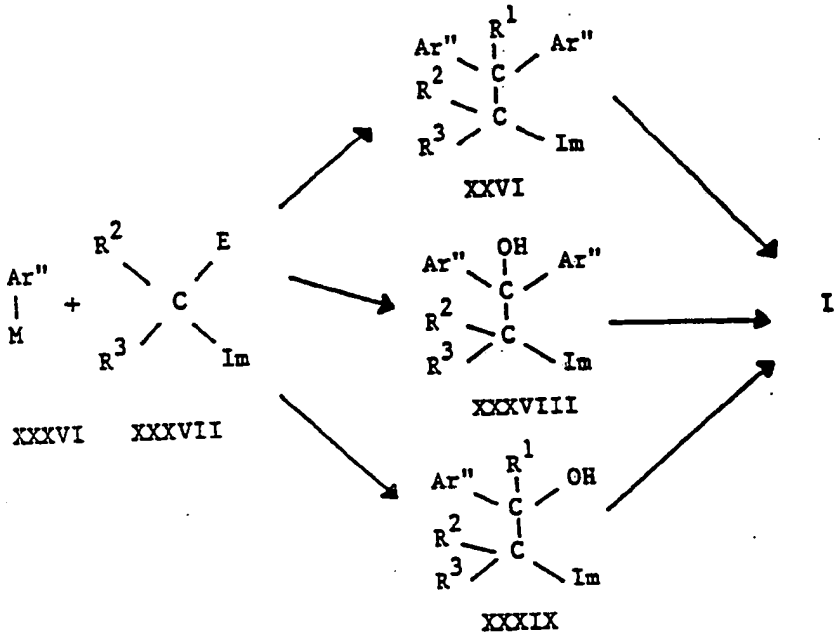
and X^1, X^2, Y^1, Y^2, R^1 to R^{10} possess the values defined above.

The preparation of the organometallic derivative XXXIV is effected in conventional manner, either by transmetallation, or by acid-base reaction of the compound (Ar)(Ar')(R^1) C-H with a strong base such for example as butyl lithium or sodium amide.

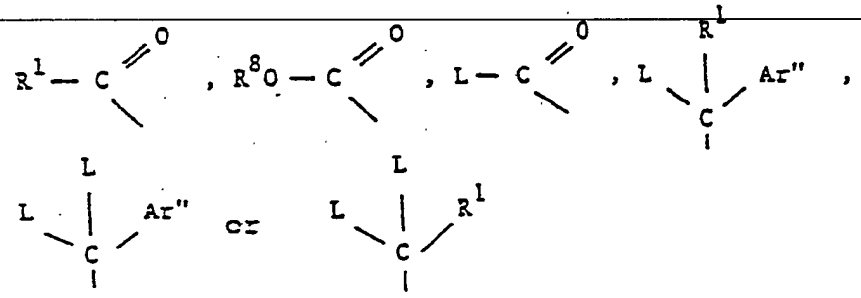
The condensation is effected by opposing the reagents XXXIV and XXXV under experimental conditions similar to those stated above in process 2 for the condensation of an organolithiated derivative with a halogenated or carbonyl derivative.

3.2. A variant of this process consists in realising the carbon-carbon bond by condensation of an organometallic derivative of formula XXXVI with a halogenated or carbonyl derivative of formula XXXVII and converting the intermediate XXVI, XXXVIII and XXXIX into a compound of formula I, in accordance with diagram 3.2. below.

Diagram 3.2.



In this diagram, E represents a halogenated and/or carbonyl group of formula

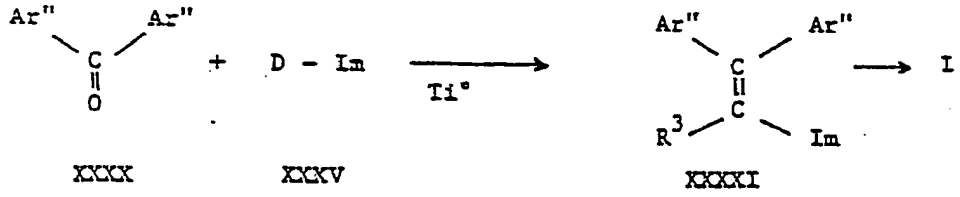


Ar" represents a group Ar or Ar' as defined above and M, L, Im and R^1 to R^{10} represent the above-stated values.

The preparation of the organometallic derivative XXXVI and its condensation with compound XXXVII are effected in accordance with known methods similar to those described above for processes 2 and 3.

3.3. Another variant of the process consists in realising the coupling of the reagents by effecting the carbon-carbon bond by condensation of two carbonyl derivatives in the presence of titanium as catalyst, followed by the conversion of the intermediate, in accordance with diagram 3.3..

Diagram 3.3.



XXXX XXXV XXXXI

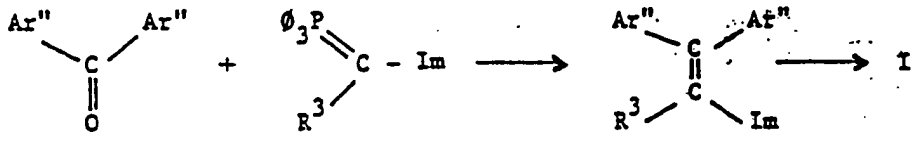
In this diagram, D represents the group $R^3-C(=O)$

and Ar", R^3 and Im possess the values defined above.

The condensation of the carbonyl derivatives is effected in accordance with a known method by heating these derivatives in an inert solvent such as dimethoxyethane in the presence of activated titanium, obtained by reaction of metallic lithium with titanium trichloride in an inert solvent.

3.4. Another variant of the above coupling consists in effecting the carbon-carbon bond by condensation of a carbonyl derivative of formula XXXX with a phosphorus ylide of formula XXXXII followed by the conversion of the intermediate XXXXI into a derivative of formula I, according to diagram 3.4..

Diagram 3.4.



XXXX XXXXII XXXXI

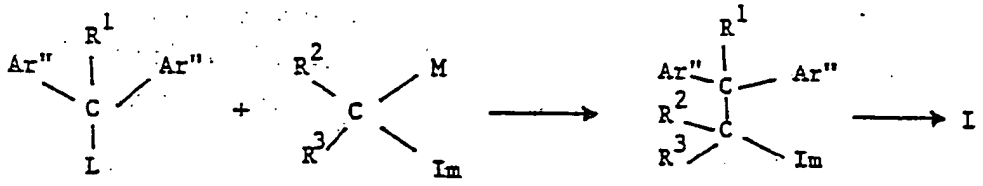
Ar", Im and R^3 possess the values already defined and Ø represents the phenyl group.

The condensation of the carbonyl derivative with the phosphorus ylide is effected under anhydrous conditions, possibly with slight heating, by opposing the reagents in dimethyl sulphoxide, followed by hydrolysis of the reaction medium. The ylide itself is obtained by treating the corresponding alkyltriphenylphosphonium halide with a strong base such as sodium hydride in anhydrous dimethyl sulphoxide.

3.5. Of course the functional groups in each of diagrams 3.1., 3.2., 3.3. and 3.4. are interchangeable and and these process variants, which are effected under the same experimental conditions as those described above, are technically equivalent to the methods 3.1., 3.2., 3.3. and 3.4..

By way of illustration such a variant is represented in diagram 3.5..

Diagram 3.5.



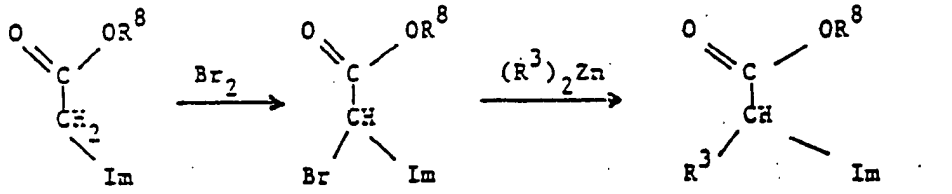
XXXXIII XXXXIV XXVI

In this diagram, Ar", L, M, Im and R^1 to R^3 possess the values defined above.

The deprotection of the imidazole group and, if appropriate, the complementary conversion of the obtained intermediate, protected or not at the level of the imidazole group, likewise take place by the same reactions as those already described for processes 1 and 2, especially by dehydration, hydrogenation, reduction, alkylation, arylation or halogenation followed by alkylation, arylation or dehydrohalogenation.

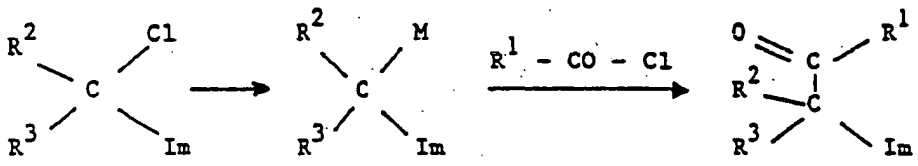
The derivatives and the reagents utilised for this process are either commercially available or easily obtained by conventional methods from available starting materials.

Thus for example derivative XXXVII (E : $R^8O - \overset{O}{\overset{\|}{C}} -$) is obtained from a 4(5) - (alkoxycarbonylmethyl) imidazole by bromination followed by an alkylation according to the following diagram :



XXXXV XXXXVI XXXVII (R^2 : H)

The compound of formula XXXVII (E : $R^1 - \overset{O}{\overset{\|}{C}} -$) is obtained for example from a suitable alkyl halide by metallation followed by a reaction with an alkanoyl halide according to the following diagram :



XXXXVII XXXXVIII XXXVII

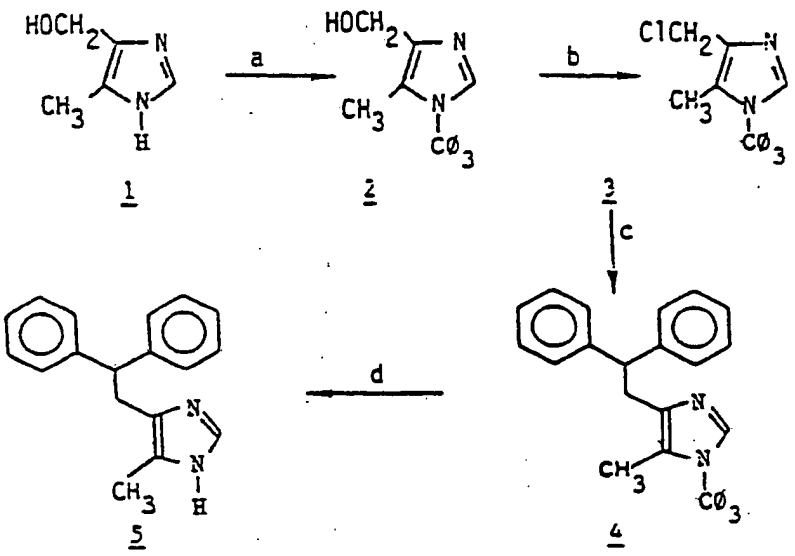
In the above diagrams the symbols R^1 to R^8, M and Im represent the same values as those defined above.

The selection of the process for preparation of derivatives of formula I, of the reagents and of the experimental conditions is effected in such manner as to keep intact the part of the substrate which does not participate in the envisaged transformation or conversion.

Some detailed examples of preparation of the derivatives according to the invention are given below with the purpose of non-limitatively illustrating the particular characteristics of the processes according to the invention.

Example 1.

Synthesis of 4(5) - (2,2-diphenylethyl)-5(4)-methyl imidazole 5.



(Ø = phenyl)

a) Synthesis of 1-trityl-4-hydroxymethyl-5-methylimidazole 2.

71.6 g of chlorotriphenylmethane are added, progressively and under nitrogen, to a solution of 12.5 g of 4(5)-hydroxymethyl-5(4)-methylimidazole 1 and 75 ml of triethylamine in 150 ml of anhydrous DMF, previously cooled (ice bath). At the end of the addition the reaction mixture is stirred for 16 hours at room temperature. It is then poured into 1.2 l of water and

extracted with chloroform. The organic phase is washed with water, dried over magnesium sulphate and evaporated under reduced pressure. The residue is dispersed in 1 l of ether and cooled (ice bath), 1-trityl-4-hydroxymethyl-5-methylimidazole 2 crystallizes in the form of a white solid which is filtered and washed successively with hot isopropanol and ether.

M.p. 231 - 232°C.

b) Synthesis of 1-trityl-4-chloromethyl-5-methylimidazole 3.

0.41 ml of thionyl chloride are added drop by drop to a solution of 2 g of 1-trityl-4-hydroxymethyl-5-methylimidazole 2 and 0.83 ml of triethylamine in 28 ml of anhydrous benzene. After 45 minutes of stirring at room temperature the solution is filtered and the precipitate is washed with benzene.

The combined organic phases are dried over calcium chloride and evaporated under reduced pressure. Thus 1-trityl-4-chloromethyl-5-methylimidazole 3 is obtained in the form of a yellow solid which is immediately used in the following step.

c) Synthesis of 1-trityl-4-(2,2-diphenylethyl)-5-methylimidazole 4.

22.5 ml of a 0.5 M solution of the lithiated derivative of diphenylmethane in THF are added drop by drop to a suspension of 0.5 g of cuprous cyanide (CuCN) in 10 ml of anhydrous THF cooled to -78°C (solid carbon dioxide, acetone). At the end of the addition the reaction mixture is allowed to warm up to room temperature for some minutes.

Then it is cooled again to -78°C and a solution of 1-trityl-4-chloromethyl-5-methylimidazole 3 in 10 ml of anhydrous THF is added thereto. After stirring for

an hour at -78°C the reaction mixture is kept at -20°C for 48 hours. Then 30 ml of an aqueous 10% ammonia solution saturated with ammonium chloride are added and the mixture is extracted with ether.

The organic phase is washed with water, dried over potassium carbonate and evaporated under reduced pressure. The residual oil is dispersed in heptane and cooled with an ice bath. This causes the precipitation of a yellow solid which is recrystallised in isopropanol.

The 1-trityl-4-(2,2-diphenyl ethyl)-5-methylimidazole 4 is so obtained in the form of a white solid.

M.p. 205 - 206°C.

d) Synthesis of 4(5) - (2,2-diphenyl ethyl)-5(4)-methylimidazole 5.

A solution of 0.83 g of 1-trityl-4-(2,2-diphenylethyl) -5-methylimidazole 4 in 20 ml of 90% acetic acid is refluxed for 15 minutes. It is then poured into a mixture of ice and water and extracted with dichloromethane.

The resulting aqueous phase is rendered alkaline by means of an aqueous solution of 10 N sodium hydroxide and extracted with chloroform. The combined organic phases are evaporated and the residue is dried by addition of toluene and azeotropic distillation. The resultant oil is dispersed in ether, which yields 4(5)-(2,2-diphenylethyl)-5(4)-methylimidazole in the form of a white solid which is filtered and dried under reduced pressure.

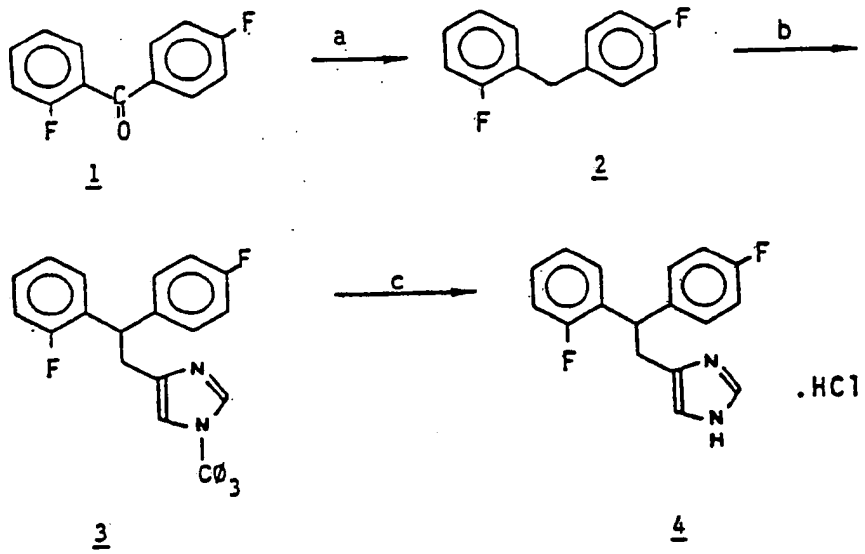
M.p. 217 - 218°C.

Elementary analysis:

		C	H	N
$C_{18}H_{18}N_2$	% calculated	80.7	7.0	10.5
	% found	81.0	6.9	10.3

Example 2.

Synthesis of 4(5) -[[2-(2-fluorophenyl)-2-(4'-fluorophenyl)]ethyl]imidazole (hydrochloride) 4.



a) Synthesis of 2,4'-difluorodiphenyl methane 2.

100 ml of ethanol and 1.1 g of 10% palladium on carbon are introduced into a Parr apparatus of 1 l. Then a solution of 10.90 g (50 mmol) of 2,4'-difluorobenzophenone in 100 ml of the preceding solvent and 1 ml of a saturated solution of hydrochloric acid in methanol are added. The mixture is hydrogenated under a pressure of 2.75 bars for 2 hours at 0°C. The obtained medium is filtered then evaporated to dryness under reduced pressure.

The product thus obtained is purified by distillation under reduced pressure.

B.p. 66 - 70°C / 4.10^{-1} mbar.

b) Synthesis of 4-|[2-(2-fluorophenyl)-2-(4'-fluorophenyl)]-ethyl|-1-tritylimidazole 3.

Sodium is added in small portions into a reactor containing 50 ml of liquid ammonia and swept by a slight current of nitrogen, until a persistent blue coloration is obtained. A few crystals of iron-III nitrate are added to the solution, folowed by a supplementary quantity of 253 mg of metallic sodium. The medium is stirred at -75°C for 30 minutes, before the slow addition of a solution of 2.04 g (10 mmols) of 2,4'-difluorophenylmethane in 5 ml of ether then, after a further half hour, a solution of 3.21 g (9 mmols) of 1-trityl-4-chloromethylimidazole in 20 ml of THF. Accordingly the ammonia is allowed to evaporate spontaneously, then 30 ml of water are added to the residue, which is then extracted three times with methylene chloride. The combined extracts are dried and evaporated to dryness under reduced pressure.

The product is introduced as such into the following step.

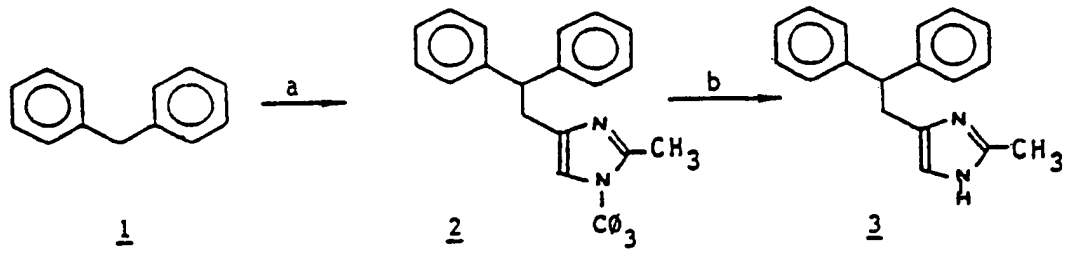
c) The preceding tritylated derivative is mixed with 20 ml of acetic acid at 90%, heated for 5 minutes to reflux temperature then evaporated to dryness under reduced pressure. The residue is shared between methylene chloride and 5% aqueous sodium hydrogen carbonate. The aqueous phase is again extracted twice and the combined organic extracts are dried and evaporated. The residue is taken up in ether and the solution is saturated with anhydrous gaseous hydrochloric acid. The precipitated hydrochloride is filtered and precipitated again in a mixture of acetonitrile and ether. M.p. 141 - 141.5°C.

Elementary analysis :

	C	H	N
$C_{17}H_{14}F_2N_2.HCl$			
% calculated	63.7	4.7	8.7
% found	63.6	4.7	8.8

Example 3.

Synthesis of 4(5) - (2,2-diphenylethyl)-2-methylimidazole 3.



1 2 3

a) Synthesis of 4-(2,2-diphenylethyl)-2-methyl-1-tritylimidazole 2.

Under an inert atmosphere (nitrogen), 16.8 ml of t.-butyllithium (1.7 M solution in hexane) are added to 4.30 g (26 mmols) of diphenyl methane dissolved in 50 ml of THF. The mixture is cooled by means of an ice bath then again a solution of 5.00 g (12.9 mmols) of 4-chloromethyl-2-methyl-1-tritylimidazole in 30 ml of THF is added. After one night of stirring at room temperature, 40 ml of a saturated aqueous solution of sodium chloride and then 100 ml of water are added to the medium. The aqueous phase is extracted three times with methylene chloride then the combined extracts are dried and evaporated to dryness under reduced pressure. The residue is used as such in the following step.

b) The above obtained tritylated derivative is refluxed for 5 minutes in 100 ml of 90% acetic acid. The solution obtained is evaporated to dryness under reduced pressure. 200 ml of water are added to the residue and the resulting suspension is filtered. The filtrate is neutralised by means of 5% aqueous sodium carbonate then extracted three times with methylene chloride. The evaporation of the combined extracts furnishes a solid which is purified by crystallisation in acetonitrile.

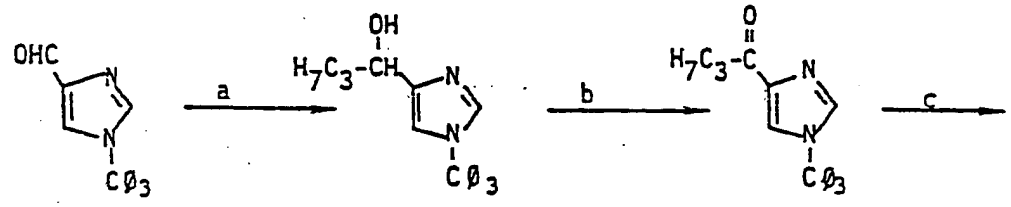
M.p. 168 - 170°C.

Elementary analysis :

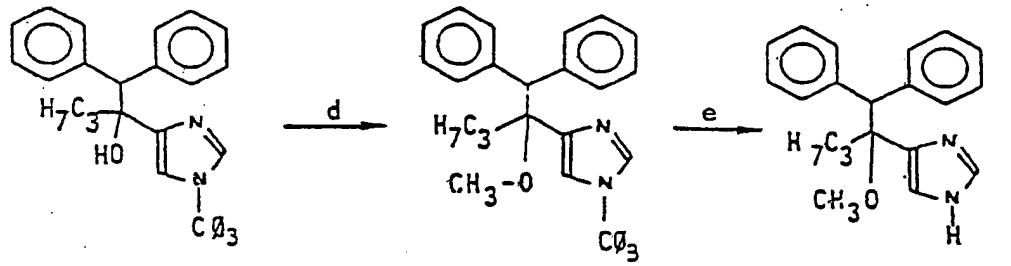
		C	H	N
$C_{18}H_{18}N_2$	% calculated	82.4	6.9	10.7
	% found	82.3	6.9	10.7

Example 4.

Synthesis of 4(5) - [2-(1,1-diphenyl-2-methoxy)-pentyl] imidazole 6.



1 2 3



4 5 6

a) Synthesis of 4-[1-(1-hydroxy-butyl)] -1-tritylimidazole 2.

To 0.80 g (32.6 m moles) of magnesium turnings kept under an inert atmosphere (nitrogen) there are added an iodine crystal then a solution of 4.00 g (2.95 ml; 32.6 mmols) of 1-bromopropane in 25 ml of anhydrous diethyl ether, at such a speed that the mixture is kept at reflux temperature. At the end of the addition the medium having returned to room temperature is cooled by means of an ice bath. Then a solution of 5.50 g (16.3 mmols) of 1-trityl-4-imidazole carboxaldehyde in 50 ml of THF is added slowly. The mixture is stirred for 2 hours at room temperature, then 100 ml of a saturated aqueous solution of ammonium chloride are added. The aqueous phase is extracted with diethyl ether and, after drying, the extracts are evaporated to dryness under reduced pressure. The residue, which crystallises spontaneously, is recrystallised in ethyl acetate.
M.p. 154 - 155°C.

b) Synthesis of 4-butanoyl-1-trityl-imidazole 3.

150 ml of dioxane and 11.00 g (10 eq.) of manganese dioxide are added to 4.75 g (12.4 mmols) of alcohol 2. The mixture is heated for 1 hour to reflux temperature then returned to room temperature before being filtered over a bed of celite. The filtrate is evaporated to dryness under reduced pressure and the residue is recrystallised in cyclohexane.
M.p. 134 - 136°C

c) Synthesis of 4-[2-(1,1-diphenyl-2-hydroxy)-pentyl]-1-tritylimidazole 4.

A solution of 4.30 g (25.8 mmols) of diphenylmethane in 50 ml of THF is prepared in inert atmosphere (nitrogen) then cooled in an ice bath. First 16.7 ml of

butyllithium of a 1.7 M solution in hexane and then, drop by drop, a solution of 4.90 g (12.9 mmols) of the previous ketone 3 in 50 ml of THF, are added slowly. The resultant mixture is stirred for 2 hours at room temperature and then 50 ml of a saturated aqueous solution of ammonium chloride and 100 ml of water are added. Extraction with ethyl acetate followed by evaporation of the previously dried extracts yields alcohol 4 which is recrystallised in cyclohexane.

M.p. 196 - 198°C.

d) Synthesis of 4-[2-(1,1-diphenyl-2-methoxy)-pentyl] -1-tritylimidazole 5.

6.00 g (11 mmols) of 4 and 60 ml of THF are mixed under inert atmosphere (nitrogen). To this mixture, cooled in an ice bath, there are added 7 ml of butyllithium (1.7 M in hexane), then 3.12 g (1.38 ml; 22 mmols) of methyl iodide. The mixture is stirred at room temperature for 0.5 hour before the addition of 50 ml of a saturated aqueous solution of ammonium chloride and 50 ml of water.

The aqueous phase is extracted with diethyl ether. The extracts are dried and evaporated to yield a residue which is used as such in the following step.

e) The previous tritylated derivative is treated with 30 ml of 66% aqueous acetic acid and the mixture is heated to reflux temperature until complete dissolution. The mixture is returned to room temperature, then cooled in a bath of ice water. The precipitate which is formed is filtered. The filtrate is neutralised by means of 5% aqueous sodium carbonate and extracted three times with ether.

The extracts are dried and evaporated to dryness under reduced pressure. The residue is finally recrystallised in acetonitrile to yield the desired product 6.

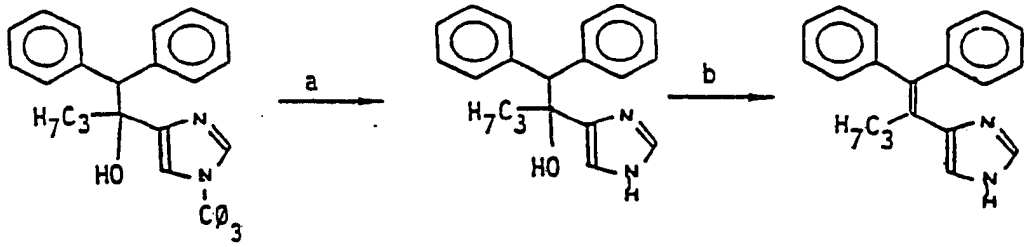
M.p. 161 - 163°C.

Elementary analysis :

	C	H	N
$C_{21}H_{24}N_2O$			
% calculated	78.7	7.6	8.7
% found	78.9	7.6	8.8

Example 5.

Synthesis of 4(5)-[(2,2-diphenyl-1-n.propyl)-ethenyl]-imidazole 3.



1 2 3

a) Synthesis of 4(5) -[2-(1,1-diphenyl-2-hydroxy)pentyl]-imidazole 2.

A mixture of 5.00 g (9.1 mmols) of 4-[2-(1,1-diphenyl-2-hydroxy)-pentyl]-1-tritylimidazole 1 (see example 4) and 20 ml of 90% aqueous acetic acid is heated for 1 hour at reflux temperature. After return to room temperature the mixture is evaporated under reduced pressure. The residue is taken up in water and the aqueous phase is extracted with methylene chloride. The combined extracts are dried and evaporated to dryness under reduced pressure. The crude product (2) thus obtained is used as such in the following step.

b) 110 ml of hydrobromic acid (33% in acetic solution) are added to 3.00 g (8.8 mmols) of the alcohol 2. The mixture is stirred for 16 hours at room temperature, then it is diluted with 100 ml of water and neutralised with 1 N aqueous NaOH. The aqueous phase is extracted with diethyl ether. The combined extracts are dried and evaporated to dryness under reduced pressure. The residue is purified by recrystallisation in ethyl acetate.

M.p. 187 - 188°C.

Elementary analysis :

		C	H	N
$C_{20}H_{20}N_2$	% calculated	83.3	7.0	9.7
	% Found	83.3	7.1	9.7

Example 6.

Synthesis of 4(5) -[2-(1,1-diphenyl) pentyl]imidazole 2.

1 2

0.80 g (2.8 mmols) of 4(5) -[(2,2-diphenyl-1-n.propyl)-ethenyl]imidazole (see example 5) are hydrogenated in 200 ml of ethanol for 6 hours in the presence of 0.13 g of 10% palladium over carbon, at 2.72 bar and 70°C. The reaction medium is filtered and the filtrate is evaporated to dryness under reduced pressure. Diethylether is added to the residue and the insoluble part is filtered and eliminated. The filtrate is evaporated to dryness under reduced pressure and the residue is puri-

fied by crystallisation in heptane.

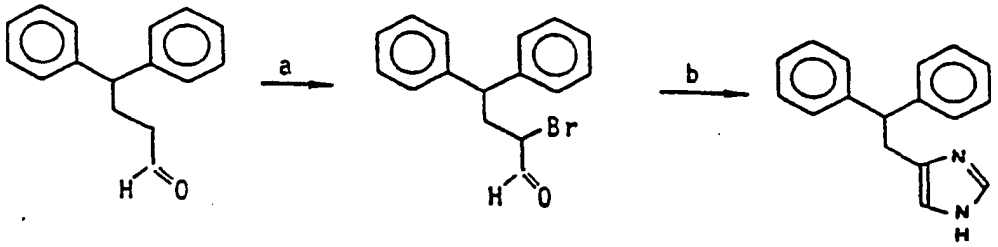
M.p. 116 - 119°C.

Elementary analysis :

		C	H	N	H_2O
$C_{20}H_{22}N_2$ (1.7% H_2O)	% calculated	81.3	7.7	9.5	-
	% found	81.5	8.0	9.2	1.7

Example 7.

Synthesis of 4(5) - (2,2-diphenylethyl)-imidazole 3.



1 2 3

a) 45.6 g of 4,4-diphenylbutanal 1 (0.2 mol), 200 ml of anhydrous ether and 0.7 ml of dioxane are introduced under nitrogen atmosphere into a 500 ml flask. Several drops of bromine are added to this solution. When the solution has lost colour, 10.42 ml of bromine (0.2 mol) are added drop by drop in 90 minutes at such a rate that the solution remains colourless. At the end of the addition the reaction mixture is neutralised by a saturated solution of Na_2CO_3, the etheral phase is decanted, washed 3 times with water and dried over $MgSO_4$. This solution is evaporated under reduced pressure and protected from light. The colourless oil obtained is introduced immediately into the following step.

b) 470 ml of formamide are heated to 160°C in a 1 litre flask under nitrogen atmosphere, the brominated aldehyde 2 is then added drop by drop. The mixture is heated for 4 hours at this temperature, cooled and poured into 1 litre of iced water. The pH value is adjusted to 2 by addition of concentrated HCl, the insoluble yellow solid is filtered, the aqueous phase is extracted by CH_2Cl_2 and made alkaline (pH 10) by means of 4 N NaOH. The white solid formed is filtered and recrystallised once in acetonitrile and once in toluene.

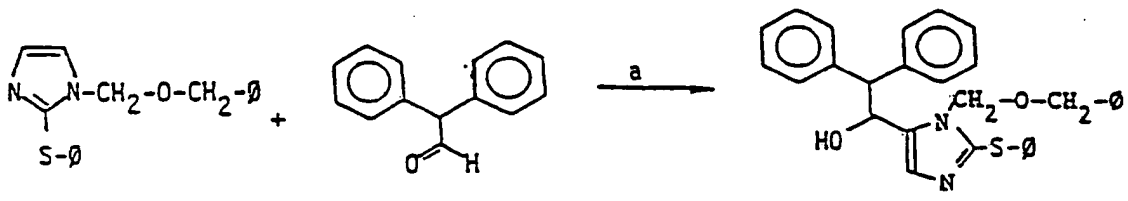
M.p. 158°C.

Elementary analysis :

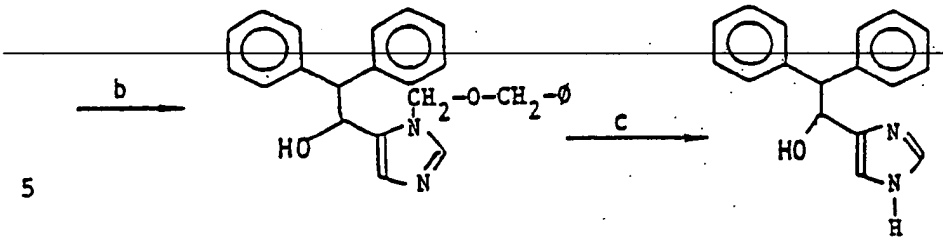
		C	H	N
$C_{17}H_{16}N_2$	% calculated	82.2	6.5	11.3
	% found	82.1	6.5	11.3

Example 8.

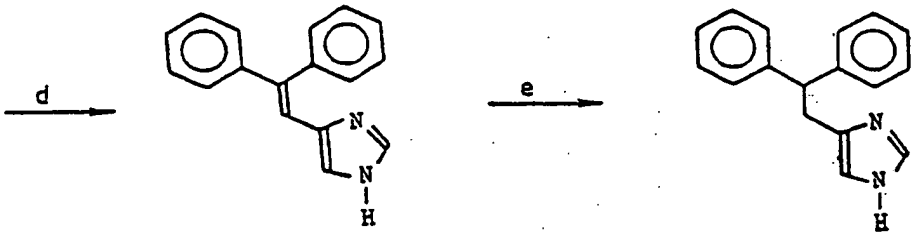
Synthesis of 4(5) - (2,2-diphenylethyl)-imidazole.



1 2 3



4 5



6 7

a) 9 g of 1-benzyloxymethyl-2-phenylthio-imidazole 1 (30 mM) and 150 ml of anhydrous THF are introduced into a 500 ml flask under nitrogen atmosphere. Then 25.6 ml of a 1.6 molar solution of butyllithium (41 mM) are added to the solution cooled to -78°C. After two hours at -65°C, 7.1 ml of diphenylacetaldehyde (40 mM) are added and the mixture is left overnight to return to room temperature. Then a saturated aqueous solution of ammonium chloride is added. The organic phase is decanted, dried over $MgSO_4$ and evaporated. The residual oil is purified by preparative HPLC (SiO_2 / CH_2Cl_2 / CH_3OH / 100 / 1).

A white powder is obtained which melts at 60 - 61°C.

b) 5 g of 3 are brought to reflux in ethanol in the presence of 5 g of Raney nickel during 5 hours. Then the Raney nickel is filtered, the ethanol is evaporated and the residue is shared between water and dichloromethane. The organic phase washed with water is dried over $MgSO_4$ and evaporated, the obtained solid is washed with toluene.

M.p. 183 - 184°C.

c) 2 g of 4 are dissolved in a mixture of 125 ml of ethanol and 125 ml of 11 N HCl, this solution is hydrogenated at 80°C in the presence of 200 mg of Pd/C at 10%.

After absorption of one equivalent of hydrogen, the catalyst is filtered and the solvents are evaporated to dryness.

d) 700 mg of 5 are brought to reflux in 10 ml of trifluoroacetic acid. After 24 hours the trifluoroacetic acid is evaporated and the residue is introduced as such into the following step.

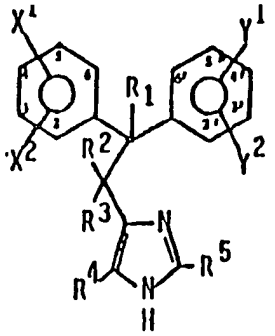
e) 700 mg of 6 are hydrogenated in ethanol at 60°C under 3.1 bars for 5 hours in the presence of 100 mg of 10% Pd/C. After absorption of one equivalent of hydrogen, the catalyst is filtered, the solvent is evaporated and the residual oil is shared between 1 N NaOH and ethyl acetate. The organic phase, washed with water, is dried over $MgSO_4$ and evaporated to dryness. The solid obtained is recrystallised in toluene.

M.p. 157°C.

Table I below lists the derivatives of the above examples and other derivatives according to the invention prepared according to the processes given above.

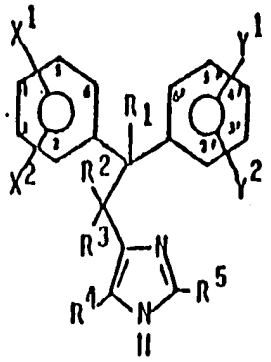
All the compounds listed in Table I give a correct C, H, N elementary analysis and their structures have been verified by N.M.R. spectroscopy and mass spectrometry.

TABLE I.



Compound No.	Code CP	X^1	X^2	Y^1	Y^2	R^1	R^2	R^3	R^4	R^5	Melting point (°C)	Recrystallisation solvent
1	2953	H	H	H	H	H	H	H	H	H	158-159	toluene
2	3414	H	H	H	H	- (1)		CH_3	H	H	166	toluene
3	3415	H	H	H	H	H	OH	CH_3	H	H	183-184	toluene
4	3476	H	H	H	H	H	H	CH_3	H	H	190	toluene
5	3506	H	H	H	H	H	OH	H	H	H	177-178	CH_3CN
6	3516	H	H	H	H	H	CH_3O	H	H	H	170	CH_3CN
7	3524	H	H	H	H	H	H	H	CH_3	H	217-218	ether
8	3540	H	H	H	H		H	H	H	H	290-300(2)(3)	EtOH
9	3588	3-CH_3	H	H	H	H	H	H	H	H	140 (3)	i.C_3H_7-OH /ether
10	3610	H	H	H	H	CH_3	H	H	H	H	153	CH_3CN
11	3640	H	H	H	H	- (1)		H	H	H	170-171	MeOH-H_2O
12	3725	2-CH_3	H	H	H	H	H	H	H	H	182 (3)	CH_3CN/ether
13	3710	2-Cl	H	H	H	H	H	H	H	H	159 (3)	CH_3CN/ether

TABLE I.



Compound No.	Code CP	X^1	X^2	Y^1	Y^2	R^1	R^2	R^3	R^4	R^5	Melting point (°C)	Recrystallisation solvent
14	3604	4-F	H	H	H	H	H	H	H	H	157	CH_3CN
15	3685	2-F	H	4'-F	H	H	H	H	H	H	141-141,5 (3)	CH_3CN / ether
16	3661	2-CH_3	5-CH_3	H	H	H	H	H	H	H	171 (3)	CH_3CN
17	3688	4-OCH_3	H	H	H	H	H	H	H	H	142	CH_3CN
18	3649	H	H	H	H	-(1)		$n.C_3H_7$	H	H	187-188	ethyl acetate
19	3658	H	H	H	H	H	H	$n.C_3H_7$	H	H	116-119	heptane
20	3668	H	H	H	H	H	CH_3O	$n.C_3H_7$	H	H	161-163	CH_3CN
21	3726	4-CH_3	H	H	H	H	H	H	H	H	219 (3)	CH_3CH / ether
22	3727	3-CH_3	4-CH_3	H	H	H	H	H	H	H	107 (3)	CH_3CH
23	3756	4-OCH_3	H	4'-OCH_3	H	H	H	H	H	H	178-179(3)	CH_3CN
24	3757	2-CH_3	4-CH_3	H	H	H	H	H	H	H	245-246(3)	isopropanol
25	3766	H	H	H	H	H	H	H	H	CH_3	168-170	CH_3CH
26	3808	H	H	H	H	H	CH_3O	H	H	CH_3	177-179	CH_3CN

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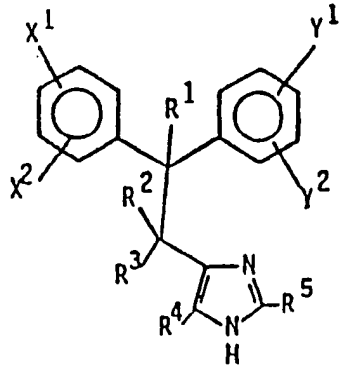
TABLE I.

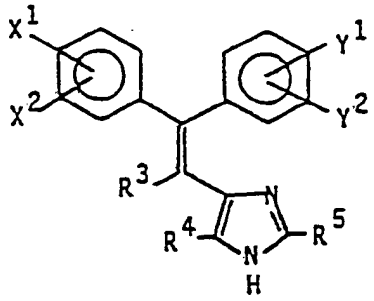


Compound N°	Code CP	X^1	X^2	Y^1	Y^2	R^1	R^2	R^3	R^4	R^5	Melting point(°C)	Recrystallisation solvent
27	4059	2-F	6-F	H	H	H	H	H	H	H	193 (3)	CH_3CN
28	4083	2-F	H	H	H	H	H	H	H	H	161 (3)	CH_3CN
29	4084	4-C_6H_5	H	H	H	H	H	H	H	H	192	CH_3CN
30	4152	2-COOH	H	H	H	H	H	H	H	H	258 (dec)	DMF
31	4226	2-$COOCH_3$	H	H	H	H	H	H	H	H	161 (3)	CH_3CN / ether
32	4253	4-COOH	H	H	H	H	H	H	H	H	212 (dec)	isopropanol

TABLE I.

Remarks.

(1) : The substituents R_1 and R_2 together represent a carbon-carbon bond in such manner that these compounds of formula I correspond to the following formula I' :



(I')

(2) : decomposition.

(3) : hydrochloride.

The products according to the invention have been subjected to a series of tests in order to examine their biological activities.

The acute toxicity was studied after oral administration to mice. The products to be tested, suspended in a 1% tragacanth gum mucilage, were administered by means of an intragastric probe to groups of three male mice which had fasted since the preceding day. The doses tested are a function of the effect observed and can vary from 3,000 to 3 mg/kg or less. The mortality was recorded for 15 days. The lethal dose for 50% of the animals (LD_{50}) was calculated according to the method of J.Litchfield and F.Wilcoxon, J.Pharmacol.Exp.Ther., 96, 99 (1949) and expressed in mg/kg. The results are indicated in Table IV, pp.59-60.

The effect of the products on the behaviour of the animals is observed until 5 to 6 hours after the treatment indicated above and after 24 hours, using a method derived from that of S.Irwin, described by R.A.Turner, Screening Methods in Pharmacology, Chapter 3, pages 22-34, Academic Press, 1965.

If anomalies are noted, the observation is prolonged and smaller doses are tested.

No important side effect upon the behaviour was observed for the majority of the compounds.

The activity of the compounds according to the invention with respect to the α-adrenergic receptors was determined in vitro according to a method deriving from the works of B.R.Rouot et al., Life Sci., 25, 769 (1979) and of D.U'Prichard et al., Mol.Pharmacol., 13, 454 (1977).

This method consists in measuring the binding to the receptor on rat brain homogenates, by marking by means of a specific tritriated ligand placed in competition with the product to be tested.

In this precise case the binding to the α_1-adrenergic receptors was measured by means of 1.6 nM of ^{3}H-WB 4101 and the binding to the α_2-adrenergic receptors by means of 0.7 nM of ^{3}H-p. aminoclonidine, the non-specific binding being determined by 1,000 nM of phentolamine.

The results are given in Table IV, pp. 59-60 and are expressed in the form of percentage of inhibition of the specific binding at 10^{-7} molar. They demonstrate that the compounds according to the invention present no significant affinity for the α_1 receptors since the percentage of inhibition of the specific binding on the α_1 receptors is generally negligible.

On the other hand the considerable percentage of inhibition of the specific binding on the α_2-adrenergic receptors presented by a large number of these compounds indicates that the derivatives according to the invention are in general endowed with a considerable affinity for the α_2 receptors.

Among these derivatives, the compounds n° 1, 9, 13, 27 and 28 present a particularly high activity.

The selectivity of this affinity for the α_2 receptors is a characteristic property of the compounds according to the invention which opens up very interesting perspectives as regards their therapeutic applications.

The α_2 antagonist and α_2 agonist activity of the compounds according to the invention was determined upon isolated organs according to a model described by G.M. Drews, Br. J.Pharmaco., 64, 293 - 300 (1978).

This model is based upon the principle that the stimulation of the cholinergic nervous transmissions of the guinea pig ileum causes the liberation of acetyl choline, which in turn causes contractions of the ileum.

The stimulation of the α_2-adrenergic receptors inhibits the activity of the cholinergic nerve and consequently reduces all response resulting from a stimulation of the latter. Thus the contractions of the ileum induced by electric stimulation of the tissue are inhibited by clonidine, an α_2 agonist, in proportion to the dose. This inhibition is specifically displaced by the α_2 antagonists and not by the α_1 antagonists.

The method utilised can be summarised as follows : three dose - response curves to clonidine are established at an interval of 60 minutes. Two concentrations of the product to be tested are added successively 10 minutes before the realisation of the second and third clonidine curves. Next, after washing, a dose - response curve is established with the product to be tested.

The dose - response curves are calculated as a percentage of the maximum inhibition obtained for the first curve.

In this system the products having an α_2 antagonist activity displace the dose - response curve to clonidine.

The α_2 antagonist activity, expressed in pA_2 value, is calculated according to J.M.Van Rossum, Arch.Int.Pharmacodyn., 143, 299 - 300 (1963).

A reduction of the contractions induced by the tested product alone indicates an α_2 agonist effect. This activity is expressed in - log ED_{50} (the - logarithm of the concentration of the product giving 50% of the maximum inhibition obtained with clonidine).

The results, summarised in Table IV below, indicate that the products according to the invention in general display a highly selective α_2 antagonist activity and that some compounds display a certain α_2 agonist activity.

The antagonist effect of the compounds according to the invention on peripheral vascular α_2 receptors was demonstrated in biological experiments carried out on pithed rats.

The α_2 antagonist activity of the compounds is evaluated by the inhibition of the pressor effect of a specific α_2 agonist agent (BHT 920; 30 µg/kg i.v.) according to a method described by J.C.Van Meel et al., J.Pharmacol. Exp.Ther., 219, 760 - 767 (1981).

The compound to be tested is administered at 1 mg/kg i.v. The inhibiting effect of the compound tested compared with the increase of the pressure caused by BHT 920 is determined and expressed as percentage of inhibition.

Any direct hypertensive (= α_2 agonist) activity of the compounds under test can likewise be detected.

In this test, several compounds according to the invention have shown themselves very active as α_2 antagonist agents, in particular compounds Nos. 1, 4, 7, 9, 12, 13, 14, 15, 17, 21, 22 and 23.

The activity of the compounds according to the invention on the level of the central nervous system has been demonstrated under four experimental conditions by examining the effect upon :

- the antihypertensive action of clonidine,
- the locomotive depression induced by clonidine,
- the serotoninergic system
- convulsions caused by bicuculline and by 3-mercaptopropionic acid.

In the first study, carried out upon unanaesthetised spontaneously hypertensive rats (SHR rats), the inhibition of the antihypertensive action of clonidine by compounds according to the invention is determined.

This activity of clonidine is described as resulting from an interaction with α_2 adrenergic receptors of the central nervous system.

In this test, SHR rats are treated with the product (1 mg / kg p.o.) before sub-cutaneous administration of clonidine (50 µg / kg).

The arterial pressure is measured in the region of the median coccygeal artery according to J.Roba, A.F.De Schaepdrijver, Exp.Anim., 4, 147 - 162 (1971).

In parallel, the pressure of SHR rats treated solely with placebo and SHR rats treated with clonidine is measured.

The results, indicated in Table IV below and expressed as percentage of inhibition of the effect of clonidine, show that the majority of the derivatives of the invention displays a marked antagonist effect.

In the second study, the effect of inhibition of locomotive depression induced by clonidine is evaluated by means of the " Open field test " in the mouse.

Mice pretreated (n = 4) with the product to be tested, at doses of 1 to 10 mg / kg p.o., receive clonidine (0.3 mg / kg p.o.) two hours later. Thirty minutes after the administration of clonidine the animals are placed in a rectangular " Open field " of 47 x 53 cm, the floor of which is divided into 36 boxes of about 8 x 9 cm.

The number of boxes through which the animal goes in 3 minutes and the number of rearing episodes are noted.

Under the effect of clonidine, an α_2 agonist, there is inhibition of the locomotive activity and of the rearing activity in the mouse. Among the compounds according to the invention, compound No.1 has proved particularly active. This compound opposes the effect of clonidine upon the locomotive activity as from the dose of 1 mg / kg p.o. and upon the rearing activity as from 3 mg / kg p.o..

Furthermore the experimental results summarized in table II hereafter show that repeated administration of compound n° 1 for 14 days maintains the activity against clonidine in the open-field test in mice at the same level as after acute administration, thus proving that α_2-blocking activity is maintained after chronic administration, and that accumulation does not occur since the activity has disappeared 24 hours after withdrawal of the drug.

Table II : Effect of compound n°1 on the locomotive activity in the Open-field test (a).

Treatment by cpd n°1	Time since last administration of the drug	% inhibition of the effect of clonidine on the locomotive activity in mice
acute admin.	1 h.	52
chronic admin.	1 h.	59
	24 h.	3
	72 h.	5

(a) Groups of 5-6 mice each were treated with the drug to be tested (3 mg/kg p.o.) either twice daily for 14 days (chronic) or with one single dose (acute).
Hypomotility induced by clonidine (0,15 mg/kg i.p.) was determined 1h, 24h and 72h after the last treatment with the drug and the result is expressed in % inhibition of the effect of clonidine provoked by the drug.

In the third study the effect of the compounds of the invention on the serotoninergic system is determined.
It is known that after chronic administration anti-depressants are able to modulate the so-called serotoninergic syndrome induced by the 5-HT agonist 5-methoxy-N,N-dimethyltryptamine (2 mg/kg i.p.) in mice. This syndrome is increased after withdrawal of the anti-depressant (E.Friedman, et al., Eur.J.Pharmacol., 89, 69-76, 1983).
In this study the compounds to be tested were administered to mice at the dose of 3 mg/kg p.o. either once (acute) or twice a day during 2 weeks (chronic). The response to stimulation by 5-methoxy-N,N-dimethyltryptamine (head twitches) was observed 1, 24 and 72 hours after the last treatment.
The results obtained for compound n° 1 are summarized in table III hereafter.

Table III : Effect of compound n° 1 on the serotoninergic syndrome induced in mice.

Treatment	Time since the last treatment	Head twitches / 5 minutes % (1)
vehicle only		100
cpd n° 1 (at 3 mg/kg p.o.)		
acute	1 h.	171
chronic	1 h.	278
	24 h.	210
	72 h.	211

(1) % = per cent head twitches compared to the ones of the vehicle treated group.

From these data it results that compound n° 1 at 3 mg / kg p.o. is clearly able to modulate the serotoninergic response as is shown by the results obtained 72 hours after the last treatment.

In the fourth study the anti-convulsive effect was examined on convulsions, especially the tonic extension of the paws, caused by intravenous injection of 0.7 mg / kg of bicuculline three hours after treatment with the product to be tested, administered by oral route at the dose of 10 mg / kg to 10 mice. The anti-convulsive activity is expressed in the form of percentage of animals protected. The results are given in Table IV below and indicate that several compounds display a significant anti-convulsive activity.

The anti-convulsant effect of the compounds has also been tested with respect to the tonic extension induced by 3-mercaptopropionic acid (3-MPA) (120 mg / kg subcutaneously) in mice.

The compounds to be tested are administered orally at 100 mg / kg 30 minutes before the test. The activity was tested on a group of 5 mice; if more than 1 mouse was protected, a second group of 5 mice has been tested. The results are expressed in % of the animals which have been protected (= % protection). In this test, several compounds of the invention present a potent anti-convulsant effect (compounds n° 1, 3, 10, 13, 16, 24, 27, 28 and 29).

Compound N° (1)	LD_{50}	% inhibition of the specific binding (2) at 10^{-7} M for		α_2 antagonist activity (pA_2)	α_2 antagonist activity (- log ED_{50})	α_2 antagonist effect (% inhibition of the antihypertension effect of Clonidine)	anticonvulsive effect (versus Bicuculline) (% protection)
		α_1 recept.	α_2 recept.				
1	155	17	89	8,3	5,5	50	0
2		3	43	7,3	5,6	71	20
3		0	10			67	10
4	> 300	4	5	6,5	< 5,5	68	40
5	> 300	3	2			24	30
6		0	0			62	30
7		12	23	7,3	5,7	82	20
8	1.750	0	0			28	20
9	155	4	85	7,8	5,6	92	20
10		0	6			46	27
11		6	9			48	40
12	155	0	71	7,9	5,4	78	50
13	172	7	81	8,0	5,5	46	20
14	155	0	69	7,8	5,2	82	0
15	155	7	77	7,8	5,3	75	0
16	> 300	0	31	7,0	5,7	69	20
17	350	6	78	7,9	5,0	26	10
18	270	0	0			47	50
19	350	4	15			75	40
20	> 300	0	6			62	60

TABLE IV : BIOLOGICAL DATA.

Compound N° (1)	LD_{50} (mg/kg)	% inhibition of the specific binding (2) at 10^{-7} M for α_1 recept.	% inhibition of the specific binding (2) at 10^{-7} M for α_2 recept.	α_2 antagonist activity (pA_2)	α_2 antagonist activity (- log ED_{50})	α_2 antagonist effect (% inhibition of the antihypertension effect of Clonidine)	anticonvulsive effect (versus Bicuculline) (% protection)
21	350	4	74	7,6	5,3	48	50
22	155	4	22			57	20
23		0	20			40	10
24		0	34			93	0
25		0	3			87	10
26	350	1	2				10
27	173	14	86				
28	94	8	95				
29	> 300	15	23				
30	> 300	12	1				
31		13	20				

(1) The numbers of the compounds correspond to the numbers of the compounds in Table I, indicated previously.

(2) The specific binding is the total binding less the non-specific binding.
The total binding is the binding in the absence of non-radioactive drug.
The non-specific binding is the binding in the presence of 1,000 nM of phentolamine.
The products of the invention are tested at a concentration of 10^{-7} molar.

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The products according to the invention, and more particularly product n°1, administered orally to mice, likewise display in the " Open field " test at 3 mg / kg a greater exploratory activity than that of the controls, this being manifested by an increase of the frequency of rearing.

The blocking activity of the derivatives of the invention on the adrenergic α_2 receptors at the peripheral non-vascular level has been demonstrated in vivo by examining the antagonist effect of the compounds on hyperglycaemia induced by clonidine.

The compound to be tested is administered by oral route (p.o.) at 10 mg / kg to rats, not fasting, 60 minutes before the sub-cutaneous injection (s.c.) of clonidine (0.3 mg / kg).

The group under examination includes animals treated with the products to be tested, animals which have received only placebo, both p.o. and s.c., and animals which have received only clonidine. Glucose is proportioned in blood plasma drawn 60 minutes after the s.c. injection of clonidine or placebo, with the aid of a glucose-oxidase kit (Boehringer GOD PAP).

Among the compound according to the invention, compounds Nos. 1, 3, 15 and 21 showed themselves particularly efficient against the hyperglycaemiant effect of clonidine.

In man, the compounds according to the invention can be administered by various routes and in various galenic forms.

Thus the compounds will be administered for example one to three times per day orally, at doses ranging from 1 mg to 300 mg.

By way of non-limitative illustration, some examples of galenic forms are given below, in which the compound according to the invention, being the active compound, is

designated by the letter A. As active compound it is possible to use for example one of the following compounds :

4(5) - (2,2-diphenyl ethyl) imidazole,

4(5) -[(2,2-diphenyl-1-methyl) ethenyl] imidazole,

4(5) -|[2-(3-methylphenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(2-chlorophenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(4-fluorophenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(2-fluorophenyl)-2-(4'-fluorophenyl)] ethyl | imidazole,

4(5) -|[2-(4-methoxyphenyl)-2-phenyl] ethyl | imidazole,

4(5) -[(2,2-diphenyl-1-n.propyl) ethenyl] imidazole,

4(5) -[2-(1,1-diphenyl)-pentyl] imidazole,

4(5) -[2-(1,1-diphenyl-2-methoxy) pentyl] imidazole,

4(5) - (2,2-diphenylethyl)-2-methylimidazole,

4(5) - (2,2-diphenylethyl)-5(4)-methylimidazole.

4(5) -|[2-(2-fluorophenyl)-2-(6'-fluorophenyl)]ethyl | imidazole,

4(5) -|[2-(2-fluorophenyl)-2-phenyl] ethyl | imidazole,

4(5) -|[2-(4-biphenyl)-2-phenyl] ethyl | imidazole,

4(5) - [1-(2,2-diphenyl)-propyl] imidazole,

4(5) -|[2-(2-methylphenyl)-2-(5'-methylphenyl)]ethyl| imidazole

4(5) -|[2-(2-methylphenyl)-2-(4'-methylphenyl)] ethyl| imidazole.

Tablets.

a.	A.		25	mg
	microcrystalline cellulose		100	mg
	pregelatinised starch		50	mg
	colloidal silicon oxide		1	mg
	magnesium stearate		2	mg
b.	A.		200	mg
	polyvinyl pyrrolidone		7.5	mg
	maize starch		50	mg
	lactose		50	mg
	microcrystalline cellulose		50	mg
	magnesium stearate		2.5	mg

Injection.

A.		5	mg
sodium chloride		8	mg
purified water	ad	1	ml

Topic - transdermal form.

A.		5	g
carbomer ®		1	g
sodium hydroxide	ad	pH	6.5
purified water	ad	100	g

Drops.

A.		5	g
phosphate buffer	ad	pH	6.5
sodium saccharinate		0.5	g
purified water	ad	100	ml

Rectal form.

A.		50	mg
polysorbate 80 ®		20	mg
witepsol ®	ad	2	g

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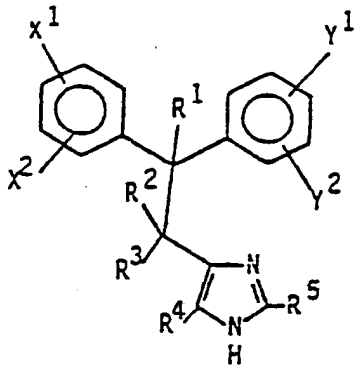
CLAIMS

1) Imidazole derivative of general formula I



I

wherein :
X^1, X^2, Y^1 and Y^2, which may or may not be identical, represent hydrogen, a fluorine, chlorine or bromine atom, a linear or branched alkyl radical C_1, C_2 or C_3, a linear or branched alkoxy radical C_1, C_2 or C_3, a carboxy group, an alkoxy[C_1, C_2 or C_3]- carbonyl group or a phenyl group,
R^1 represents hydrogen, a methyl or phenyl group,
R^2 and R^3, which may or may not be identical, represent hydrogen, a hydroxyl group, a linear or branched alkyl group C_1, C_2, C_3, C_4, C_5 or C_6, a linear or branched alkoxy group C_1, C_2, C_3 or C_4,
R^1 and R^2 can together likewise represent a carbon-carbon bond,
R^4 and R^5, which may or may not be identical, represent hydrogen or a linear or branched alkyl radical C_1, C_2 or C_3 , also the geometric and optical isomers and

mixtures thereof and the various possible tautomers and salts of addition formed with pharmaceutically usable acids.

2) Derivative according to Claim 1, characterised in that in general formula I, X^1, X^2, Y^1 and Y^2, which may or may not be identical, represent hydrogen, an atom of fluorine or chlorine, a methyl, methoxy or phenyl radical.

3) Derivative according to Claim 1 or 2, characterised in that all or more than two of the groups X^1, X^2, Y^1 and Y^2 are different from hydrogen.

4) Derivative according to Claim 3, characterised in that at least X^2 and Y^1 represent hydrogen.

5) Derivative according to Claim 1 or 2, characterised in that X^1, X^2, Y^1 and Y^2 represent hydrogen.

6) Derivative according to Claim 1 or 2 characterised in that one or both of the groups X^1 and Y^1 represent an atom of fluorine

7) Derivative according to any one of Claims 1 to 6, characterised in that R^1 represents hydrogen or a methyl group and R^2 represents hydrogen or a hydroxyl, methyl or methoxy group.

8) Derivative according to any one of Claims 1 to 6, characterised in that R^1 and R^2 together form a carbon-carbon bond.

9) Derivative according to any one of Claims 1 to 8, characterised in that R^3 represents hydrogen or a linear or branched alkyl group C_1, C_2, C_3 or C_4.

10) Derivative according to any one of Claims 1 to 9, characterised in that R^4 and R^5, which may or may not be identical, represent hydrogen or a methyl group.

11) Derivative according to any one of Claims 1 to 10, characterised in that R^1, R^2, R^4 and R^5 represent hydrogen.

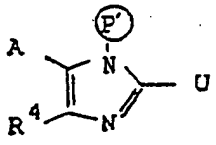
12) Derivative according to any one of Claims 1 to 11, characterised in that X^1, X^2, Y^1, Y^2, R^1, R^4 and R^5 represent hydrogen.

13) Derivative according to Claim 1, characterised in that it is selected from the group formed by the following compounds :

4(5) - (2,2-diphenylethyl) imidazole
4(5) - [(2,2-diphenyl-1-methyl) ethenyl]imidazole
4(5) - [[2-(3-methylphenyl)-2-phenyl]ethyl]imidazole
4(5) - [[2-(2-chlorophenyl)-2-phenyl]ethyl]imidazole
4(5) - [[2-(4-fluorophenyl)-2-phenyl]ethyl]imidazole
4(5) - [[2-(2-fluorophenyl)-2-(4'-fluorophenyl)]ethyl] imidazole
4(5) - [[2-(4-methoxyphenyl)-2-phenyl]ethyl]imidazole
4(5) - [(2,2-diphenyl-1-n.propyl) ethenyl]imidazole
4(5) - [2-(1,1-diphenyl)-pentyl]imidazole
4(5) - [2-(1,1-diphenyl-2-methoxy) pentyl]imidazole
4(5) - (2,2-diphenylethyl)-2-methylimidazole
4(5) - (2,2-diphenylethyl)-5(4)-methylimidazole
4(5) - [[2-(2-fluorophenyl)-2-(6'-fluorophenyl)]ethyl] imidazole
4(5) - [[2-(2-fluorophenyl)-2-phenyl]ethyl]imidazole
4(5) - [[2-(4-biphenyl)-2-phenyl] ethyl] imidazole
4(5) - [1-(2,2-diphenyl)-propyl] imidazole
4(5) - [[2-(2-methylphenyl)-2-(5'-methylphenyl)]ethyl] imidazole
4(5) - [[2-(2-methylphenyl)-2-(4'-methylphenyl)]ethyl] imidazole

14) Imidazole derivative as described above, especially in the examples given.

15) Process for the synthesis of derivatives of formula I as defined in one of claims 1 to 14, characterised in that a compound of formula



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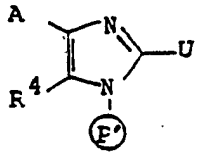
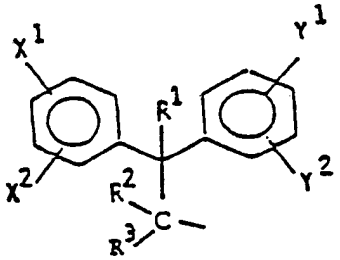


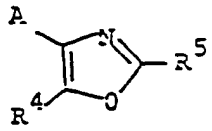
wherein A represents the group



and X^1, X^2, Y^1, Y^2, R^1, R^2, R^3 and R^4 have the meanings as defined in claim 1,
Ⓟ represents hydrogen, an hydoxy group or a protective group of the nitrogen atom, and U represents hydrogen, the group R^5 as defined in claim 1, an amino group, a mercapto group, an alkylthio group, a phenylthio group or another group easily substituable by hydrogen,
is transformed into a compound of formula I by substitution of Ⓟ, if Ⓟ is different from hydrogen, and of U, if U is different from hydrogen or R^5, by an hydrogen atom by means of one or more of the reactions adequately chosen from the group comprising an hydrolysis, an hydrogenation, a desulphurization, an hydrogenolysis, a diazo-

tation, an oxydation, an acidolysis in aqueous or non aqueous medium, a reduction, a treatment with an hydride followed by an hydrolysis and optionally by treatment with sodium acetate in acetonitrile at elevated temperature or a treatment with $TiCl_3$, a dehydration or a dehydrogenation.

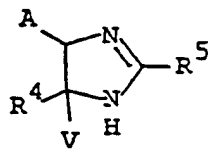
16) Process for the synthesis of derivatives of formula I as defined in one of claims 1 to 14, characterized in that a compound of formula XVI



XVI

wherein A, R^4 and R^5 are as defined in claim 15 is converted into a compound of formula I by heating the oxazole XVI in the presence of ammonia or of formamide.

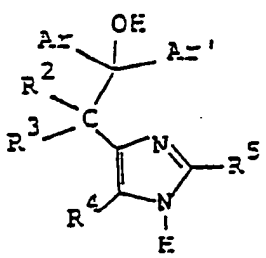
17) Process for the synthesis of derivatives of formula I as defined in one of claims 1 to 14, characterized in that a compound of formula



wherein A, R^4 and R^5 have the meanings defined in claim 15 and V represents hydrogen, a dialkylamino group, a morpholino group, or a sulphurcontaining group R^9-S(O)$_n$- in which R^9 represents a methyl or tolyl group and n has the values 0 or 2, is transformed into a compound of formula I by one or more reactions carried out preferably in

an inert solvent and adequately chosen from the group comprising an oxydation at moderate temperature, a dehydrogenation at elevated temperature in the presence of a dehydrogenation catalyst, a desamination reaction carried out by the action of triethylamine hydrochloride or pyridine hydrochloride preferably at elevated temperature, and a desulphurization carried out by means of hydrogen in the presence of Raney nickel or another suitable catalyst.

18) Process for the synthesis of derivatives of formula I as defined in one of the claims 1 to 14 characterized in that an oxy-compound of formula



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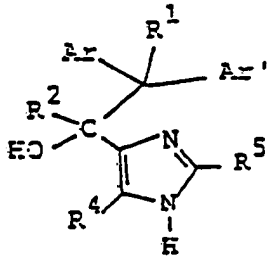

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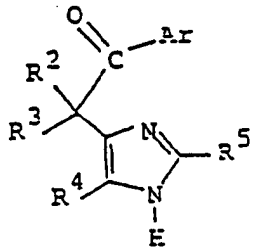

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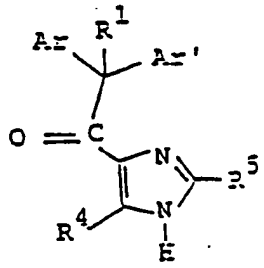
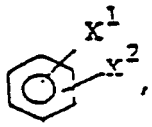
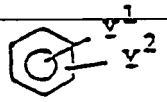
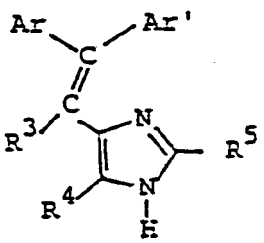


wherein Ar represents the group  , Ar' the group  and R^1 to R^5 represent the groups as defined in claim 1, is transformed into a compound of formula I by one or more reactions adequately chosen from the group comprising an alkylation reaction, an arylation reaction, a dehydration reaction, an hydrogenation reaction, an hydrogenolysis reaction, a reduction reaction, or a substitution reaction of the hydroxylgroup by an halogen atom and subsequent conversion of this halide by an alkylation or arylation or dehydrohalation so as to obtain a compound of formula I.

19) Process for the synthesis of derivatives of formula I as defined in one of the claims 1 to 14 characterized in that an ethylene derivative of formula



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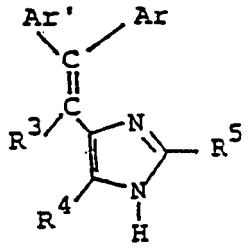
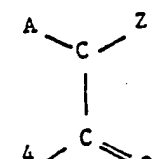
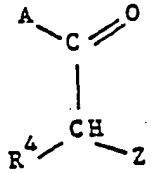


wherein Ar, Ar', R^3, R^4 and R^5 have the meanings defined in claim 18 is transformed into a compound of formula I, by one or more reactions adequately chosen from the group consisting of an hydrogenation reaction, an hydration reaction, an oxydation reaction, an alkylation reaction, or by an epoxidation reaction followed by an hydrolysis reaction.

20) Process according to any one of claims 15 to 19 for the synthesis of derivatives of formula I, as defined in one of Claims 1 to 14, characterised in that the imidazole group is formed by a condensation of a carbonyl derivative of formula IIa or IIb, the carbonyl group of which may be latent in the form of a cyclic or non-cylic acetal or thioacetal,

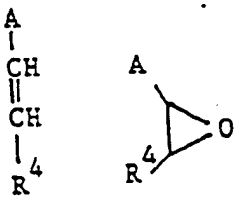


IIa



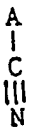
IIb

of an alkene IX, of an epoxide XI, or a nitrile XX, of an aldimine XXI, of an oxazole XVI or of an enamine XVII

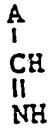


IX

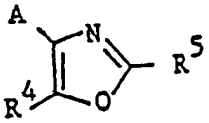
XI



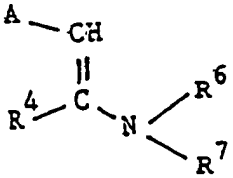
XX



XXI

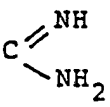
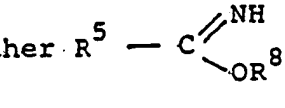


XVI



XVII

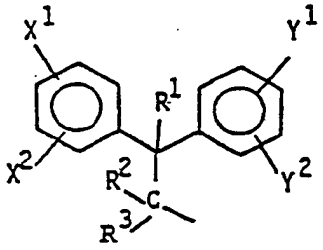
with an appropriate reagent in the presence or absence of ammonia or a solvent, at a temperature which can range up to reflux of the reaction medium, this appropriate reagent being selected from the group formed by an amide $R^5 - CONH_2$

an amidine  , an iminoether  ,

cyanamide $CN - NH_2$, guanidine $NH_2 - \underset{\underset{NH}{\|}}{C} - NH_2$,

~~ammonium or alkali thiocyanate, formaldehyde in the~~ presence of ammonia, nitrosonium tetrafluoroborate in the presence of a nitrile $R^5 - CN$, tri-n.butylstannyl-tetrazole, formamide, N-chloramidine $R^5 - C(=NCl)(NH_2)$, or an isonitrile of formula XXII $R^9 - S(O)_n - CH_2 - N = C$ (XXII), wherein

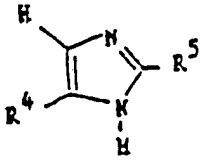
A represents the group



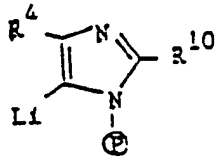
Z represents a hydroxyl radical, an oxo radical, an atom of halogen, an amino group or an alkanoyloxy radical, and X^1, X^2, Y^1, Y^2, R^1 to R^5 being defined above, R^8 represents an alkyl group C_1-C_3, R^9 represents a methyl or tolyl group, n being 0 or 2, and NR^6R^7 represents a dialkylamino or morpholino group, followed by the conversion of any intermediate into a derivative of formula I, by dehydration, hydrogenation, oxidation, dehydrogenation, reduction, irradiation, hydrogenolysis, hydrolysis ,deamination or by desulphurisation.

21) Process according to one of claims 15 to 19 for the synthesis of derivatives of formula I, as defined in any one of Claims 1 to 14, characterised in that an imi-

dazole group of Formula XXVIII or presented in the form of an organo-lithium compound of formula XXV



XXVIII

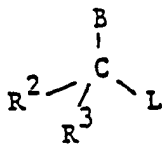


XXV

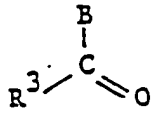
wherein Ⓟ represents a protective group chosen from the group comprising alkyloxymethyl, benzyloxymethyl, dialkoxymethyl, trimethylsilylmethyl, [2-(trimethylsilyl) ethoxy]methyl, trityl, vinyl, benzyl, N,N-dialkylaminosulphonyl, 2-chloroethyl, 2-phenylsulphonylethyl, diphenylmethyl or [(bis-trifluoromethyl)(4-chlorophenoxymethoxy)] methyl group,

R^{10} represents the group R^5 or a protective group, being a phenylthio or alkylthio group,

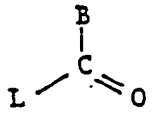
is grafted on to a substrate of formula XXIV, XXX or XXXI



XXIV

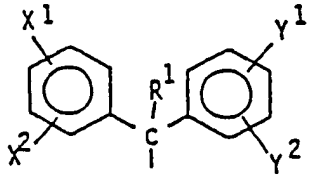


XXX



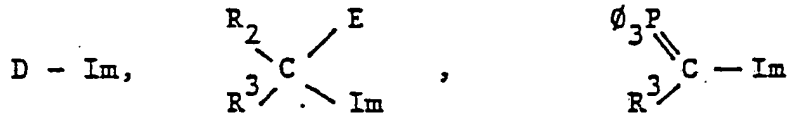
XXXI

wherein B represents the group



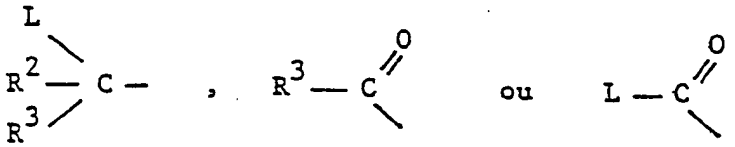
L represents an atom of halogen, an O-tosyl or O-mesyl group, X^1, X^2, Y^1, Y^2 and R^1 to R^5 having the values defined in claim 1, the reagents being opposed in an inert solvent preferably at low temperature, or a mixture of the reagents XXVIII and XXX being irradiated in the presence or absence of an inert solvent, followed by a conversion of any intermediate into a compound of formula I by a dehydration, hydrogenation, reduction, alkylation or by hydrogenolysis and a deprotection of the imidazole group.

22) Process according to one of Claims 15 to 19 for the synthesis of derivatives of formula I as defined in one of claims 1 to 14, characterised in that a derivative of formula XXXV, XXXVII or XXXXII

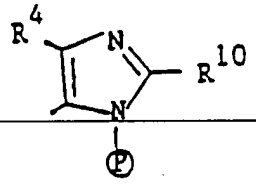


XXXV XXXVII XXXXII

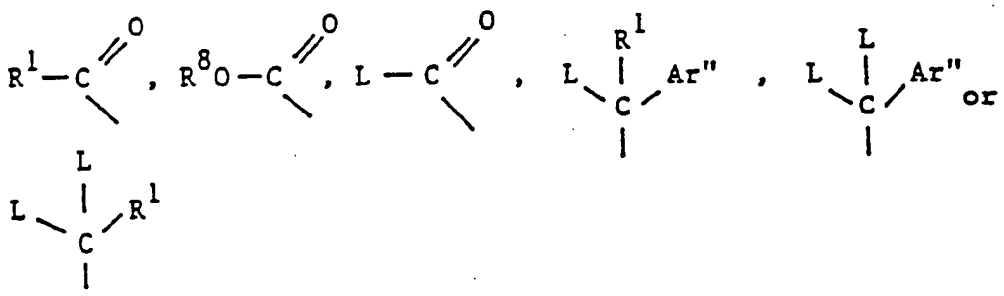
wherein D represents a group

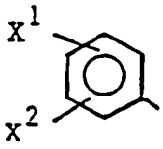
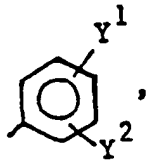


wherein L represents an atom of chlorine, bromine or iodine, Im represents the imidazole group of formula

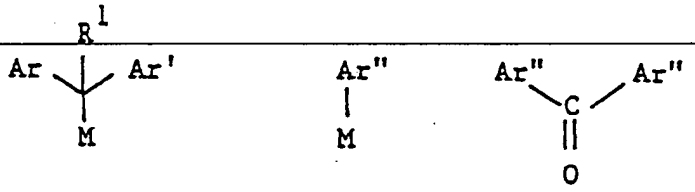


wherein Ⓟ represents a protective group as defined in claim 21,
E represents a carbonyl and /or halogenated group of formula



wherein Ar" represents a group Ar or Ar', Ar being a group  and Ar' being a group  ,

Ø represents the phenyl group, and L, X^1, X^2, Y^1, Y^2 and R^1 to R^{10} being defined above in claims 20 and 21, is coupled in an inert solvent in the presence or absence of a catalyst with a suitable reagent selected among the compounds of formula XXXIV, XXXVI or XXXX



XXXIV XXXVI XXXX

wherein M represents an atom of lithium, sodium or potassium, or a radical containing magnesium, zinc, copper or titanium and Ar, Ar' and Ar" are as defined above, followed by a conversion of any intermediate into a compound of formula I by dehydration, hydrogenation, reduction, hydrogenolysis, alkylation, acylation or halogenation followed by an alkylation, arylation or a dehydrohalogenation and/or a deprotection of the imidazole group, account being taken of the fact that the functional groups D or E and M of a substrate-reagent pair are interchangeable and lead under the same experimental conditions to product I.

23) Process according to one of claims 15 to 19 for the synthesis of derivatives of formula I as defined in one on claims 1 to 14, characterised in that a derivative of formula I in which R^5 represents hydrogen and which is protected at the level of the nitrogen atom by a group Ⓟ defined in claim 21 is converted into a derivative of formula I in which R^5 is different from hydrogen, by lithiation of the carbon atom in the 2 position of the imidazole group, followed by an alkylation by means of a reagent of formula R^5 L in which L represents a halogen or an O-tosyl or O-mesyl group, followed by deprotection of the imidazole group.

24) Pharmaceutical composition, characterised in that it comprises at least one of the compounds of formula I or one of its salts of addition with a pharmaceutically utilisable acid according to one of claims 1 to 14, whether or not associated with an appropriate pharmaceutical excipient and another therapeutic agent.

25) Pharmaceutical composition according to claim 24, characterised in that it is presented in the form of a lozenge, granules, tablet, capsule, solution, syrup, emulsion, suspension, gel or suppository.

26) Process for the utilisation of derivatives of formula I or pharmaceutically utilisable salts according to one of claims 1 to 14 in the treatment of depressive and degenerative ailments of the central nervous system, certain forms of hypertension, epilepsy, dyskinesia, obesity, gastroduodenal ulcer or cardiac or sexual inadequacies, also as anti-convulsant, anti-migraine, anti-thrombotic, anti-asthmatic, diuretic, anorexigenic or anti-diabetic agent.

27) Process for the utilisation of the derivatives of formula I or of the pharmaceutically utilisable salts according to one of claims 1 to 14, for the treatment of depressive ailments.

28) Process for the utilisation of the derivatives of formula I or of the pharmaceutically utilisable salts thereof according to one of claims 1 to 14 as anti- epileptic agents.

29) Process for the utilisation of derivatives of formula I according to any one of claims 26 to 28, characterised in that they are administered once to thrice per day by oral route at the dose of 1 mg to 300 mg.

European Patent Office

EUROPEAN SEARCH REPORT

0194984
Application number

EP 86 87 0010

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
A	US-A-4 281 141 (MERRIT-PIOCH)		C 07 D 233/64 A 61 K 31/415 C 07 D 233/58
A	EP-A-0 034 474 (FARMOS YHTYMÄ OY)		
D,A	EP-A-0 034 473 (FARMOS YHTYMÄ OY)		
E	EP-A-0 165 779 (ELI LILLY) * Pages 1-6; page 7, example 3; page 8, lines 16-18 *	1-7,9-14,24,25	

TECHNICAL FIELDS SEARCHED (Int Cl 4)

C 07 D 233/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	06-05-1986	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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